2nd Talk at Café Prückel

Flame Out

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Resolution, memory effect and organ crosstalk in inflammatory processes resulting from environmental, metabolic, infection-, pain- or cancer-based stress

Is there a scientific discovery that impressed you in the last year regarding this area of research? Any leading laboratory that inspires you?

Knapp: What impressed me most this year was probably all this single-cell RNA-seq data that came out of multiple labs, among which some prominent labs, especially in Israel. It is also impressive that they found cell types that were not known before and that play a role not only in inflammation but also in homeostasis. The lab that inspires us is, of course, Ido Amit and his whole gang at the Weizmann Institute that publishes five *Cell* papers a year, in addition to those in *Nature, Science* and so on. I think that is really top, top, top. And the second person that impressed me was Yasmine Belkaid. Our Landsteiner Lecturer investigates, among other things, how commensal bacteria shape the immune system in a way that immune cells – in her case in the skin, really commensal-specific immune cells – are required to initiate repair. I think these are quite revealing and impressive findings.

Binder: I agree with Sylvia. I think this single-cell sequencing data has been really very insightful. It tells us how heterogeneous the inflammatory processes in different tissues are, and I think that it will be the basis for many studies to come. I am sure Robert will likely comment about the interface between clonal hematopoiesis and inflammation, which is something that excites me a lot. How much cellular metabolism can actually control and direct the inflammatory response has been an evolving picture in the last years. So when cells are acting and operating during resolution, there is a different metabolic program that is turned on. There is a number of papers that have contributed to the better understanding of this, particularly in the context of sterile inflammation, how for example accumulation of lipids can actually change the response to the same ligands. I think that is something that teaches us a lot and that we will spend a lot of work on in the next years.

Kralovics: As Christoph mentioned, I am coming from a different angle. I am a cancer geneticist and last year was quite remarkable in linking clonal hematopoiesis and leukemia evolution to major changes in inflammatory signaling: two papers from mouse modeling, one from Abdel Wahab's lab at the Memorial Sloan Kettering Cancer Center that was published in *Cancer Cell*, show mutation in splicing factors. Splicing factor mutations are a huge class of very interesting, mutually exclusive mutations that occur across all the myeloid malignancies but also in solid tumors. And nobody knew how the gene defects that are downstream of these splicing aberrations can converge and exert the same kind of phenotype. It turns out that the phenotype somehow funnels into activation of NF-kappaB signaling. And one gene in particular, MAP3K7, which was found in SF3B1-mutated mouse models. It also turns out that, when the investigators looked into patients, they found the same inflammatory signature, and again on the other type of mutation, the SRSF2 mutations, both in mouse models and in patients. The paper shows that CASP9, which is also a negative regulator of NF-kappaB signaling is somehow abrogated. That was in August last year, and right after that, there was another paper from Steven Lane's group, published in *Blood,* about DNMT3A, which is again a very common aberration. A loss of DNMT3 or some point mutation, again linked to NF-kappaB signaling. So, NF-kappaB signaling now becomes a center of attention for all these chronic myeloid malignancies. And this is a common theme that adds a little bit of additional

data to the story that came out several years back on TET2 deficiencies. So, essentially, TET2, the splicing factor mutations, DNMT3A, all somehow converge on inflammatory signaling. And the beauty of these studies is that these defects are not only found in cancer patients, but as Christoph said, they are some of the earliest aberrations that turn polyclonal hematopoiesis into monoclonal, and that you know, is a very frequent phenotype in the elderly population. So, apparently, in the population of people aged about 70, between 5–10% of these supposedly healthy individuals are already clonal and have an increased risk of thrombosis. This was published in the New *England Journal of Medicine* by Benjamin Ebert's group and is now the major focus in the hemato oncology field. This is how we are somehow converging with all the groups that study very basic processes of inflammation. The trigger of inflammation is not oxidation of lipids, it's not a pathogen, but a somatic mutation. You actually have some intrinsic trigger of inflammatory signaling, just by loss of epigenetic regulators or presence of an oncogene.

Binder: Well, we don't know that. It's the response that may be altered, but in fact, when you think about it, TET2 and DNMT3, they do opposite things, but both converge. So, maybe what they do here has nothing to do with their original function.

Kralovics: You are right, because inflammatory signals are so broad and so highly regulated.

Binder: And maybe that's one explanation for why some individuals are more susceptible to, say, oxidized lipids or other triggers of inflammation. What I think is so interesting about this is, when considering personalized treatment or personalized medicine, clonal hematopoiesis, or the status of clonal hematopoiesis, may be one of the ways to stratify patients, to decide whether or not they should receive anti-inflammatory therapy. I think that is a major advance, at least when considering chronic inflammation.

Bergthaler: What excited me the most? I think it kind of dovetails with what has been said: our better appreciation of tissue complexity. Basically, how different cell types interact with each other through different means and how non-immune cells contribute to the immune system – so, the role of parenchymal cells wherever there are fibroblasts in the skin or hepatocytes in the liver – and how all of these cells interact and communicate with one another. I often think of the technological advances that have been made. Single-cell sequencing is one of them. But I think there are other approaches as well that are very exciting, including imaging approaches. In terms of labs that inspire us, there are researchers, such as Ruslan Medzhitov, who really are conceptual thinkers at the forefront, attempting to identify the evolutionary basis for what's happening in inflammatory responses. I think that is very inspiring. Sometimes what is needed then, is actual experimental data to prove or to back this up, but I think it allows us to think beyond and out of our box. What I am also excited about – at least I came across this twice in two papers – are weird cellular memory effects. In this case, T cells that you take out of a mouse, then you expose them to a drug – which is done, for example, in a paper by Erica Pearce – and then you put these cells back into a mouse. So the drug has been washed out, and yet, if you look months later, you can clearly distinguish those cells that have been treated with a drug compared to the control. I wonder whether this is classical epigenetics or maybe there is more going on and this is potentially connected to trained immunity.

What are the scientific hypotheses that we should all try to tackle together?

Kralovics: Well, our mouse models are centered around modeling hematological malignancies. And here we have two mouse models, where the JAK2-V617F mutation and the CALR mutations are knocked in. In one of these models, in a longer follow-up of mice, fibrosis develops. And of course, fibrosis is a rather severe complication in these patients, and it is a consequence of inflammatory processes. According to one of our hypotheses we formulated during our faculty recess in the summer, this may be a much broader phenomenon, because oftentimes inflammation is rather systemic. So, it's not a completely crazy idea to believe that you have inflammation induced by an oncogenic mutation., So, this is something we started to formulate into project concepts. We ordered the mouse models, we added two additional mouse models, the SF3B1 knock-in and the TET2 knock-out, and these could then be read against the background of this oncogene. So, I would say, we essentially model these processes in a very realistic genetic model. And, of course, we look for some high-penetrance, early onset myelofibrosis. And in these mice, we would like to see what other organs are affected by fibrotic damage. This would be something our groups could tackle together.

Bergthaler: So, where do you see concrete links to labs at CeMM to help you tackle this question of fibrosis?

Kralovics: Well, of course, Sylvia and you directly. Of course, the two organs that might be affected are the lung and the liver.

Bergthaler: What I find particularly exciting as an opportunity, is when we think about the human patient. There probably isn't a single patient with just one disease. They are always present in co-morbidities. So what is, I guess, one of CeMM's strengths and what our Strategic Collaborative Program "Flame Out" is all about, is basically trying to integrate and combine different diseases and to see how they influence each other, sometimes not even driven by a hypothesis, but just simply doing it because we can, and because those labs are available at CeMM. And fibrosis could be such an umbrella to look at different options.

Kralovics: Another aspect is, that our hypothesis is more about trying to generalize things, but maybe, such a general hypothesis is not applicable to all patient groups. We might find those particular cases, perhaps 1–5% of the patients, that develop particular complications, where that hypothesis actually fits. We know that the diseases are inherently heterogenous and complex. So, I think these are opportunities to understand individual patient groups stratified by molecular or other markers and to see what the underlying disease mechanisms are.

Binder: If you consider inflammation that could feed into and even promote clonal hematopoiesis, what we are interested in looking at is how diet could contribute to these TET2 mutations and other mutations associated with clonal hematopoiesis and whether this feeds into that vicious cycle, preventing resolution of inflammation.

Kralovics: And one quite interesting additional aspect that is emerging, is patients that don't have a particular molecular mutational landscape but are receiving a specific treatment like JAK inhibitors. It turns out that the cancer patients only benefit by suppressing inflammation. But these bring along a completely new set of clinical problems, like, you know, immunodeficiency or emergence of viral infections. JAK inhibitor treatment now generates a whole lot of problems, including the emergence of mutant cancer cells that are normally kept in check by the immune system. You want to treat myelofibrosis, and a new cancer emerges, that was already there. It has been shown that the burden prior to therapy was low.

Knapp: Of course, if you suppress some inflammation.

Bergthaler: How long do you administer these JAK2 inhibitors?

Kralovics: Usually the patients benefit for up to three years, but then there is some sort of resistance to them, and you need to take a break. The drug is withdrawn and then re-introduced. The problem is that this drug was approved for myelofibrosis with splenomegaly and patients benefit miraculously. Splenomegaly resolves within weeks of JAK inhibitor therapy. This is primarily when the spleen is not actually infiltrated by the tumor cells. And if you suppress inflammation, the splenic architecture changes to a certain degree, but the content of tumor cells does not. So it is truly some sort of response by the spleen to certain cytokine stimulation that changes its structure making it no longer penetrable to the cells, and it just grows large, which is a major problem. With splenomegaly, the life quality of the patient drops. Extramedullary hematopoiesis is usually at the pinnacle of inflammation. In high-grade inflammation, you have fibrosis, so the fibrosis causes extramedullary hematopoiesis. It's just more progenitors in the periphery, but at that stage, you have such massive cytokine dysregulation that the spleen responds and actually becomes impenetrable or less penetrable and just grows to a massive size. So it is an inflammatory phenotype, not an infiltration of tumor cells. Of course, there is a certain turnover of clonal cells in the spleen as well. And in many other mouse models it was shown to be enough to inhibit the JAK2.

Bergthaler: What is actually the definition of inflammation? Because in the end, you say that may be something that is simply a stress response. Christoph, what are the hypotheses connected to this inflammation, deflammation theme that your lab is tackling?

One should always consider that inflammation is something good, that we have a mechanism to fight infections and to protect us.

Binder: Where I see a lot of potential for interaction is in understanding what position my lab or your lab has in this vicious cycle of non-resolving inflammation. That can teach us a lot. More specifically, I actually sent Sylvia a paper a couple of days ago which reported very strong clinical evidence for patients with pneumococcal pneumonia having a worse outcome after myocardial infarction, which is most likely associated with dysregulated resolution of inflammation. And, very specifically, that is something Sylvia and I would like to look into in more detail, because we have the expertise on both sides. And again, this leads back to the theme of chronic and acute inflammation, like bacterial and sterile inflammation: Where do they meet? How do they cross talk and what is really happening there?

Bergthaler: Do you have mouse models set up for myocardial infarctions?

Binder: We have now started to set up these mouse models for myocardial infarctions actually. A postdoc in my lab, Dimitris Tsiantoulas, learned about this in Cambridge. We also have a very good collaborator here at the Medical University of Vienna and that's the perfect setup. You ligate the coronary artery, you induce a heart attack and then you look at the healing of the infarct tissue.

Knapp: Very much in line with what Robert and Christoph said, I think what interests us – and is also linked to others – is inflammation, injury or insult at different tissue sites, that affect, for instance, the immune response in the lung, heart, liver or bone marrow. So the interconnection between these organs, not seeing everything at an organ level but at a system level, is what we call tissue memory. These effects, we are getting more and more of a glimpse into, are where I see us linked. And the coolness of CeMM, I would say, is also that we are working on these different aspects that allow us to tackle a challenge more easily.

Bergthaler: And maybe to add to this from my lab: I think, what we are increasingly trying with different projects is to have these infection models, but we really approach inflammatory changes in a rather abstract way that is basically also applicable to non-infectious diseases. In that sense, I think this could at least be a mental bridge to cancer, and to autoinflammation, although of course, the signaling pathways are not exactly identical. There are different cell types involved, but the general framework is not that different. And whether you are stressed by a virus or bacteria, or by high cholesterol, may not be that different at the end of the day. At least it is good exercise, because we don't know anything about cancer, and yet we are immersed in an institute where at least half of the groups are working on cancer. So I think this is also a synergistic opportunity for us, being at CeMM.

How would you paraphrase this in really lay terms?

Binder: I think in lay terms, I would say one should always consider that inflammation is something good, that we have a mechanism to fight infections and to protect us. But the problem is that in certain situations it can go wrong, and it can harm us. And we would like to understand why and under what conditions this protective response of inflammation – which is basically intended to kill whatever causes the injury, like a bacterial or viral infection – can become harmful in certain situations. Which means, I believe, when it sort of becomes chronic. That can also interfere with other disease entities such as clonal hematopoiesis and hematological malignancies.

Knapp: I would add that, let's say, cells of the immune system are primarily or notoriously known to fight infections and cause diseases, but in fact they are incredibly important in preventing inflammation. So, when it comes to keeping tissue healthy or maintaining homeostasis, immune cells are basically the key to healthy tissue in real life. I mean, luckily, we are not constantly infected, and this is also due to the fact that we have an immune system. But most of the time, our immune system is probably busy keeping inflammation from happening. And in the end, we die from some chronic type of inflammation. Aging is a trigger for inflammation, and immune cells are probably as important in preventing as they are in fighting infections.

Bergthaler: I guess one key word in this regard is context, because inflammation really depends on the tissue context, on the environment, on the timing, also the phase of infection of another disease. It may be harmful, it may be beneficial. Inflammation always has a bit of a negative connotation, doesn't it? But it really depends on the given disease whether the net outcome for the host is thumbs up or thumbs down in the end. That's why it is important to gather as much information as possible. I think another idea for this strategic program is for us to take our existing models, where we focus on one primary organ – the lung in the case of pneumonia, or the liver in the case of high-fat diets – but then to actually look beyond at other organs and to see how maybe this connects. And maybe people have missed parts of the puzzle simply because they looked at the obvious place, under the street lamp at night. I think that is also something where we can cross-fertilize and benefit from each other.

Binder: Evolutionarily, obviously, you are selected for certain genes or variants of genes, that protect you from bacterial infections. But now these are the same individuals that are more likely to respond to a sterile trigger and develop chronic inflammation – and this is sort of the price we pay for having a very protective genotype. I think, in addition to the germline variants that could predefine our responsiveness, the somatic mutations that have been identified now will also be more and more interesting in terms of understanding individual and personal responsiveness to both bacterial, viral, but also sterile triggers of inflammation. I think that is something we will always have to keep in mind when we study humans – the fact there is such a great variation of responses.

Knapp: It's incredibly exciting that there is this one paper that studied the different immune responses in humans in a simplified manner. And the one thing that determines most is, whether they have CMV infection, whether they are carriers of CMV or not. It's not genetics, it's CMV or some unknown viral infection that basically determines whether they respond in one way or another. There are a lot of things, we have no clue about.

Bergthaler: It's amazing how the wiring of this whole response system works and how resilient it is at the end of the day, because I think, overall, we are all pretty healthy, at least in the developed countries. We have antibiotics and so on. But it's built into our genes, yet we still don't understand how the genes interact, how the cells interact, how the organs communicate with each other, and how in most cases, evolution has selected for this to work. That's maybe not surprising, but I think we still don't understand how this is actually happening, and a better understanding will help us interfere therapeutically.

Kralovics: To explain inflammation in blood cancers in lay terms also pretty much relates to the same topic. The immune cells, you know, are generated by hematopoiesis. All the changes happening, the cancer happening in this particular tissue compartment, have or has an immediate impact on all the immune functions in these patients. And, of course, inflammation now has been recognized as a sort of major modifier of the outcome in these patients. How to intervene in this inflammation is also a major problem. You cannot just use brute force suppression, because you'll have an infection coming up or other cancers emerging. So, I think it is also about knowing how to intervene in a way that ensures preservation of the immune function to a certain degree, but eliminates, for example, morbidity resulting from fibrosis. All these issues have to be fine-tuned and we have to find ways to suppress this activation, because inflammation is hyperactivation to some stimuli, and somehow find ways to gradually intervene or intervene in a very focused manner, to get a good therapeutic effect in these patients and not to have consequences of therapy that would result in a worsening of the disease, right?

Bergthaler: Or also harnessing these evolutionary conserved mechanisms for vaccination, for example, and really exploiting what's already there.

Is there anything regarding this area that was achieved in your laboratory/at CeMM that you think is worth mentioning?

Binder: What we found was in a way exciting and added to some of our previous papers. We demonstrated that antibodies, so-called natural antibodies that protect from bacterial infections, also seem to protect us from developing venous thrombosis. So we did clinical studies in humans, where we actually found that the recurrence of thromboembolic events is associated with the titers of the same antibodies that also protect from infection. So again, that really supports the dual role of our immune system. Another thing I found very exciting was the fact that we found – which takes us back to what you pointed out, Andreas – that it's so important to integrate all tissues and all cells when we try to understand the immune system. We found that one very specific cytokine or mediator that controls B-cell development also plays an important role in controlling the inflammatory response of macrophages. So, other cells called BAFF, or B-cell activating factor, that have not been implicated in responding to that molecule before. And we found that this is very important in a way, because it is a molecule that is already therapeutically targeted by biologicals, by monoclonal antibodies.

Bergthaler: That's macrophage-intrinsic?

Binder: And we discovered this effect of BAFF on macrophages. It controls inflammation in macrophages. But so far, in the whole of literature and previously, it has only been implicated to play a role in B-cell biology, and this is why it is therapeutically targeted with monoclonal antibodies that are already given to patients with lupus to deplete B cells and get rid of autoantibodies. But what we found out is that if you deplete BAFF, you also affect the inflammatory response of macrophages and theoretically this could be harmful. So it is very important to integrate all of this, and I think that was an important piece of evidence, again demonstrating that it is very important to look at all of the effects in an integrative way and not to focus on one part of the pathway that has been implicated before.

Kralovics: So, in my lab, we participated in a large clinical trial in this particular regard. It was a phase III, where interferon was applied to the patient group that we are studying in the lab, in particular polycythemia vera. And very interestingly, you have interferons which are one of the mediators of inflammation. Essentially, if you apply interferons systemically, the stem cells mutated with this JAK2 kinase mutation disappear during the course of treatment and essentially you restore polyclonal hematopoiesis in these patients. This data is hopefully going to be published soon. In the meantime, the European regulatory agencies have approved interferon treatment as a first-line therapy for polycythemia vera, based on this trial. So this is actually one of the major developments, and it is already public, for we reported on it at the ASH (American Society of Hematology) Meeting.

Bergthaler: So what was your role in getting this approved?

Kralovics: My lab conducted the entire molecular characterization of about 300 patients on the genetic side and we looked at baseline samples and end-of-treatment samples. We also quantified the molecular response in these patients. Essentially, we showed a very global response rate, regardless of what mutations the patients carried. They all pretty much universally went into molecular remission and that was our part in the study.

Knapp: I think what we contributed last year was basically that we looked at the interplay between different immune cells acting in the maturation of the lung at or after birth. What we found is that when the lungs develop and the immune system takes over or migrates or establishes itself in a tissue, there is a very complex interplay between different immune cells. Surprisingly, we discovered cells that have been known for years, for example eosinophils or basophils, that play an important role in actually shaping the tissue environment in the lung and that there are also tissue-resident types of basophils, which were thought to be only a rare blood cell type involved in allergies. What I find exciting is that it is becoming more and more clear that these ancient or old cells we have known for years have multiple other functions we didn't know about, and that we can find them now, even in developing lungs in mice.

We not only want to find treatments, we want to understand inflammatory pathways to eventually come up with smarter therapies.

Bergthaler: We've built a lot of resources and gained a better understanding, so while we haven't published any of these things yet, I think we have a better understanding of how little we actually know when we infect a mouse with a virus, for example, and then try to see how the metabolism changes, both in the liver and in the serum. And maybe it's not surprising, but there is still very little out there for every body compartment that you try to measure these changes for; it's often different and does not correspond. And I think that's biology for you, where, of course, the same changes don't occur in the liver or in the spleen. Trying to bring the things together and trying to mechanistically understand them is difficult, but we are getting there. We also have several advanced projects in this regard, where we implicate either a connection between, for example, the liver and T cells or between inflammation and adipose fat tissue and study how this rearrangement might then modulate and fine-tune the immune response in the course of infection. So, work in progress.

Do you have the necessary tools? Anything that needs to be further developed?

Bergthaler: CeMM is very much a technology-driven place, we have – I think – great core facilities that distinguish us from other, maybe bigger institutions. I think we are effective in this regard, but do we need more tools or specific tools for the future for your projects, something you can think of that is either in development anyway or that you would like to get for the institute?

Binder: In my opinion, what we really need – and we have discussed this with Robert several times – is not some innovative technology, but a monoclonal antibody facility.

Binder: It's such an elegant way to interfere with pathways, where you introduce more subtle phenotypes and do not genetically disrupt anything, and it would be amazing if we could have some sort of facility that fast-track develops monoclonal antibodies.

Bergthaler: Because if you want to target something in the cell, you need to have monoclonal antibodies.

Kralovics: For large mammals, you need large housing facilities, which is a bit beyond CeMM's scope and ability. I talked to a couple of places, such as the Veterinary Research Institute. They even have horses, and they were thinking about camels before, and if there was some incentive for them, they would be on it. But in the meantime, I've found something much easier: rabbit facilities. My former colleague runs a rabbit-breeding facility. She supplies laboratory rabbits to more or less all of the Czech Republic. The red tape on getting protocols approved in the Czech Republic is very straightforward. It's a simple protocol, you have about two months' turnover on these applications and we could just really have antigens shipped, immunized, and get the serum and the spleens back.

Binder: What we need is a facility where we can grow these hybridomas and make a lot of these antibodies.

Kralovics: And of course, around it, the phage display or mammalian cell display technologies, because they already somehow functionally evaluate the antibodies prior to cloning. So you select clones that already come with certain binding properties. And then you have a – how shall I say – functional antibody repertoire that is basically much easier to screen. You don't need super high-throughput anymore.

Bergthaler: OK, so that was antibodies. What other technologies are you thinking of?

Binder: What do you think about CyTOF? We have been discussing this for such a long time, but in the meantime, so many papers have been published, simply doing CyTOF analysis of cells, all published in high-ranking journals. I think this is a technology that will stay around for some time, and it was probably a mistake not to invest in it.

Bergthaler: One technology I am very excited about, and that we've started to use, is metabolite tracing in vivo, so where you administer heavy isotope-labelled metabolites of your interest into a mouse and then, at a given point in time, you harvest organs, or you sort cells, and you use mass spec to see where these heavy-labelled metabolites go and how they were converted into the next metabolites of a given cycle. We've done only a few experiments so far, but I think it looks very promising. What's clear is that we will need some full-time bioinformaticians to dig deeper, but even the very first experiments show the potential. Actually those heavy-labelled metabolites are surprisingly cheap. That is not the bottleneck we initially thought it would be.

Bergthaler: We've tried a few things. At the moment glucose and arginine. And it works. So what we've done, together with the Metabolomics Facility, and where I think Kristaps has done a marvelous job in the last two years, is to set up all these new metabolite read-outs. I foresee this as one way of investigating the crosstalk between organs and in vivo, and I think that's where our expertise of proteomics, mass spectrometry, and metabolomics will come in very handy.

Knapp: Do you sort cells? How many cells do you have to sort?

Bergthaler: So far, we have done mostly bulk tissue, but we have already sorted cells. We haven't yet done the tracing mass spec on this, but ideally, you need at least 106 cells, that's why we didn't bother with sorting and used chunks of tissue instead. And that is already complex enough, if you're trying to figure out what's going on.

Binder: I think that's a very important thing and, in the context of resolution, that is when cells ingest dying cells and you want to know where the metabolites come from, it will be interesting to find out which metabolites influence the phagocyte. Is the influence coming from the dying cell?

By when, do you think, will we see this research have an impact on medical practice?

Bergthaler: I think we've already heard one example where there is a drug actually being re-purposed for a given malignancy. Robert, when do you think Interferon will be used on polycythemia vera?

Kralovics: It is already being used off-label, but now it is becoming a first-line therapy and the decision on this drug's market authorization will already be made this year, earlier this year. So this is already going to be produced and will be released for general practices and hospitals and clinicians. So it is already happening, but now it will happen on a much greater scale.

Binder: I think to some extent we are already working on translating these efforts into international collaborations, where we start smaller clinical trials to see if we can interfere with the outcome after myocardial infarction with patients by using approved immune-modulatory therapies. But that's obviously a collaborative effort – as these things always are. But what will really impact medical practice, I cannot say. It depends on the outcomes, but I think an important step we are taking, is that we are now thinking more and more of translating our findings into real, small clinical trials.

Knapp: I think we are learning a lot from many anti-inflammatory therapies that are in place, like JAK2 inhibitors. So, we can deduce and even try to figure out why something is happening, or what happens if you block a certain pathway in humans. Even though, in our case, we want not only to find treatments, we also want to understand inflammatory pathways in order to come up with smarter therapies eventually.

Binder: But we could influence the stratification of patients sooner because our insights could help identify sub-groups of patients.

Kralovics: Or whether or not stratification makes sense.

Binder: Yeah.

Kralovics: Because sometimes it doesn't.

Bergthaler: I agree, my lab does basic research, and if there is to be any direct impact, it's probably 5 to 10 years away. I think that's the reality. But better understanding of the mechanisms could indirectly influence the decisions of other programs that are maybe closer to clinical developments and patient care. So in that sense, at least for me, we do basic research and we do not claim to revolutionize clinical medicine or anything.

Binder: It depends on what you mean by "impact" on medical practice, because in a way, medical practice is being impacted all the time, because people become interested in certain findings and then they start looking at their patients differently. In a way, this is an early impact. Real impact, so whether a new drug or treatment is introduced, is obviously not so predictable.