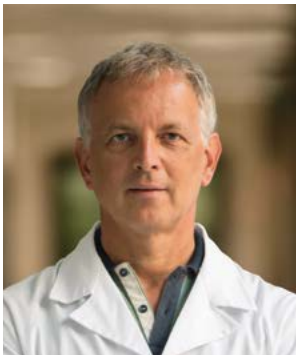
CELL & GENE THERAPY INSIGHTS

CELLULAR IMMUNO-ONCOLOGY 4.0

SPOTLIGHT

INTERVIEW

The promise of tumor-targeted gene-based delivery of immune-activating cytokines



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Q Could you give us some background on how and why Genenta Science was founded?

LN: We started from nearly a decade of clinical development of hematopoietic stem cell-based gene therapy in rare inherited diseases at the San Raffaele Telethon Institute for Gene Therapy. Through this work, we proved both the safety and efficacy of the approach, as well as the feasibility of clinical deployment up to the point of market access for these personalized and complex new therapies.

"A further advantage of gene-based delivery is sustained expression of the cytokine."

This work was also undertaken in collaboration with big pharma, which helped to establish the roadmap for advanced clinical development and market access of these gene therapies.

Based on this success, we reasoned that one could go beyond the gene replacement design – essentially, replacing a malfunctioning gene in an inherited condition – and consider the possibility of gene addition: to instruct the hematopoietic progenitors with new functions and then take advantage of their progeny, which can migrate throughout the body to deliver specific biotherapeutics in different tissues.

A major input into this came from our experience with the treatment of a neurodegenerative disease, metachromatic leukodystrophy (MLD), due to inherited deficiency of a lysosomal enzyme involved in myelin catabolism, through hematopoietic stem cell gene therapy. This was an odd concept, on paper – why would you treat a brain disease with blood stem cells? But it worked because some of the stem/progenitor cells would travel to the brain, become microglia, and then locally release the missing enzyme. Although these cells were relatively few in number, they actually made a huge difference in the clinic – they were essentially responsible for effectively treating the condition.

The success of that model prompted us to consider whether we could deliver biological products to other tissues or targets using a similar strategy – to tumors, for instance.

Those were the scientific considerations. On the business side, we decided to again leverage on our previous experience of gene therapy clinical development and take all the steps ourselves up to First in Human clinical studies, retaining full control of the process and project so that we could best steer towards our goal and create the greatest amount of value possible ahead of licensing out. We therefore explored the possibility of obtaining venture capital to fund the required stages of R&D, which we could then control in the form of a spin-out company – Genenta Science.

Q Can you tell us more about the Genenta Science platform/approach and R&D pipeline?

LN: Genenta is essentially aiming for tumor-targeted gene-based delivery of immune-activating cytokines.

Tumor-targeting means selectively delivering biotherapeutics to tumor sites – both the main tumor and potentially, to its metastases as well. 'Selectively' means that we seek to spare most of the body from systemic exposure

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to the molecule. Instead, we achieve biologically and therapeutically effective concentration at the disease site only.

This can be achieved through cell- and gene-based delivery: rather than systemic administration of a cytokine, we infuse hematopoietic stem / progenitor cells which contain an engineered gene for that cytokine. That engineering is such that the gene is highly preferentially expressed at the disease site. The stem cell progeny behave as smart vehicles, which home in on the disease site through the tumor signal which is designed to recruit myeloid inflammatory cells. Once they reach the tumor site, these inflammatory cells will then turn on the engineered gene, releasing alpha-interferon.

The safety advantages of selective delivery are clear, of course – by sparing the rest of the body exposure through systemic delivery and the associated side effects, we benefit the therapeutic index.

A further advantage of gene-based delivery is sustained expression of the cytokine, which is very important because if you do a standard pharmacological administration, you go through peaks and troughs of expression. This can often have a desensitizing effect and it can also induce side effects through the expression being either too high or too low. On the other hand, experimental models show that sustained release by cell delivery leads to a durable response within a normal physiological range.

All of this constitutes a platform: this is not a tumor-specific therapy, but rather it's a platform targeting gene-based cytokine delivery to the tumor microenvironment. As such, it has potentially broad application across many tumor types, because the microenvironment is a typical feature of all tumors and some of its features, like immunosuppression, are particularly relevant for most tumor types. And it is precisely this feature that we target through our immunotherapeutic cytokine.

Q Speaking of the tumor microenvironment, can you go a bit deeper on the challenges that presents and how Genenta Science is aiming to tackle them?

LN: There is increasing evidence of the relevance of the tumor microenvironment in shaping tumor growth and its response to therapy.

The tumor microenvironment is made up of normal host cells, which are part of the tumor mass – it comprises connective tissue stroma, vessels (which are newly formed) and a lot of immune cells that are recruited to the tumor – both innate 'inflammatory' cells of myeloid lineage and adaptive immune cells such as T cells.

The last component is supposed to be a defense mechanism of the host – the innate and adaptive cells should play together to build a protective

immune response against the tumor. However, it turns out that the inflammatory innate immune cells recruited to the tumor actually play a role for the tumor – they are co-conspirators in tumor growth, because they promote tissue remodeling to accommodate the tumor, stimulate new vessel formation (angiogenesis) and essentially disable adaptive immunity. This is a normal feature of these cells in the body because they would usually help with tissue growth and regeneration in other situations, and the tumor viciously exploits these properties.

This immunosuppressive microenvironment appears to be a major inhibitor both of the natural immune defense against the tumor and of the cellular immunotherapies developed to date. There is increasing evidence that if you can counteract this immunosuppressive activity by enhancing immune effectors, you can achieve a high rate of response to the tumor. This is essentially what the whole field of immunotherapy is trying to achieve.

Our strategy is to achieve this immune activation by tumor-targeted delivery of a key cytokine in immune activation, which is interferon alpha – a cytokine naturally released by activated innate immune cells, which promotes antigen presentation and deployment of effector T-cell activity. The presence of an interferon response gene signature within the tumor is associated with effective tumor response – achieving an interferon-like response through various strategies is one of the key lines of development in the search for more effective therapies against solid tumors. Our strategy is a novel cell- and gene-based approach, which leverages on the development of cell and gene therapies to date, and it will hopefully achieve an important effect – we have data in experimental models that is supportive of its potential efficacy and safety as well.

Q You've touched already upon the importance of extending the durability of response – can you share more details on how you will approach this very current issue for the cellular immunotherapy field?

LN: While immunotherapies, whether based on checkpoint blocking drugs or CART, are probably the first therapeutic strategies to achieve substantial rates of complete response in at least a fraction of patients in some tumors, they are still vulnerable to this immunosuppressive microenvironment. So you have a fraction of patients who do not respond to them in the first place, and then a further significant fraction of patients who are relapsing – their responses are not durable.

The main culprit for these relapses is usually this immunosuppression, which builds up in the tumor and inhibits immune activation, thereby

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allowing the tumor to escape from the adaptive immune response. This is especially the case where the adaptive immunity is directed against a single tumor antigen, as is typically the case with CART, for instance, which are designed to target a specific molecule associated with a given tumor type. They are very efficient killers, but if the tumor can manage to silence presentation of that single antigen, the tumor cells will escape.

Our strategy stimulates presentation of the endogenous tumor antigen repertoire without needing prior knowledge of it: essentially, we uncover the full spectrum of antigens present in a single tumor through the immuno-stimulatory activity of interferon. This likely leads to deployment of an immune response against multiple tumor-associated antigens, facilitating what is called antigen spreading of the response. In those circumstances, because the tumor is impacted at many different points, it's unlikely that tumor escape can occur. For this reason, this concept of antigen spreading is central to today's strategies for overcoming tumor evasion of immunotherapy, including our own.

Q What does the remainder of 2019 and 2020 hold for Genenta Science? What are your key goals and priorities?

LN: This is a key period for Genenta because we are entering clinical testing right now. We have two initial tumor targets, one solid and one hematopoietic: glioblastoma and multiple myeloma.

These two tumor types have been selected from the panel of tumors for which we have evidence of activity in preclinical tumor models, because they should provide the best therapeutic index and risk–benefit profile for First in Human testing.

Clearly, what we primarily aim to see is the safety of our strategy once deployed in the clinic, and the response to escalating dose. But we also want to see indications of its efficacy, both in biological terms through evidence of induced immune activation at the tumor site, but also hopefully in terms of actual therapeutic activity.

Typically, such trials in cell and gene therapy are designed as Phase 1/2, because they are performed in patients, not volunteers (due to the complexity of the treatment and the many unknowns, of course) and because part of the goal is to achieve some biological and therapeutic activity even upon administration of the first starting dose. We of course hope to achieve as

much benefit as possible through these studies, but beyond this, what these two concurrent studies in different tumor types should provide between them is a comprehensive analysis of the host response to our gene-based interferon delivery. Myeloma represents a hematopoietic tumor through which we can investigate the hematopoietic system in depth – that is important both for the activity but also the potential toxicity of our strategy. Glioblastoma, on the other hand, is a hard-to-reach deep brain tumor. Through that study, we can hopefully best demonstrate the capacity of our engineered cells to act as a smart vehicle to target the activity of interferon into this remote site.

Q Looking further ahead, what is your vision for Temferon's™ ongoing clinical development and commercialization, particularly in terms of its potential as both a first line therapy and a component in a combination therapy strategy?

LN: Obviously, all of this depends on us getting validation of our strategy through the early trials, but there are unique elements of our approach that I think we could exploit compared to other current cell-based gene therapies.

One of these is the fact that we don't need to replace all of the hematopoietic cells in the body. We will do a dose escalation study, but we already know from our experimental models that we only need a small fraction of engineered hematopoietic cells to deliver activity to the tumor site. Eventually, I think we could and should be moving away from the concept of a stem cell transplant, which requires conditioning prior to the treatment and which is consequently much more complex to deliver in the clinic, and move instead towards a mini-transplant or cell therapy design, which essentially will only administer engineered progenitors and require minimal conditioning. This will broaden the applicability of the strategy to many patients without the burden and limitation of the conditioning approach. If we can prove safety and efficacy in our first trial, I can see a pathway towards first line treatment due in part to this comparative ease of administration.

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Regarding improvement of efficacy, we of course hope to see as much activity and efficacy as possible in the clinic, but it's always difficult to imagine that a single agent can achieve a full and complete durable response against cancer.

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However, we know from preclinical studies that our strategy synergizes with other immunotherapy approaches. It can work in combination to achieve full immune activation – both checkpoint blockade and CART are highly empowered in the presence of this interferon mediated reprogramming of the microenvironment. We know that in the clinic, including in the tumors we're working on like myeloma and glioblastoma, CART approaches may be effective but usually don't achieve durable responses. The indication is that they will need antigen spreading to become more effective at overcoming immunosuppression. So, I think the combination of our strategy with those strategies is probably the best way to go.

And last but not least, we will continue working at the bench-to-bedside level to further implement our second-generation platform. That will be even more versatile and potentially tunable than the current platform, because it will involve the ability to adjust the level of expression of the cytokine and also to switch it on and off. We will also potentially be able to add additional cytokine payloads, making it even more efficient and tunable in the long-term. We have that work ongoing at the bench level at the current time and hope to bring it to the clinic in the future, as we deploy our strategy further.

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