TARGETS & MECHANISMS

GeNEURO GOES RETRO

By Lauren Martz, Staff Writer

GeNeuro S.A. put human endogenous retroviruses on the map as drug targets for multiple sclerosis, but new data point to a pathological role for the viruses in a much broader spectrum of diseases. Now GeNeuro is looking to academia to help explore ways of expanding the pipeline beyond its primary MS-targeted asset — once the company's platform is proven in the clinic.

Last month, GeNeuro gathered its academic collaborators and other leading researchers on human endogenous retroviruses (HERVs) at the HERVs & Disease meeting in Lyon, France, to discuss the role of HERV family members in diseases ranging from amyotrophic lateral sclerosis (ALS) to cancer.

The viruses make up about 8% of the human genome and are believed to have become inserted during the non-human primate phase of evolution. However, most are epigenetically silenced and harmless.

"It is mind-blowing to think that so much of our genome is viral," said Cedric Feschotte at the meeting. "Some viral material could be bad, but most of it is neutral. It doesn't look like it is doing anything, but there are exceptions — those needles in the haystack." Feschotte is an associate professor of human genetics at the University of Utah.

GeNeuro was spun out of bioMerieux S.A. by co-founder and CSO Hervé Perron, who discovered that HERVs could be activated in certain disease states. He found that unlike most exogenous viruses, HERVs don't replicate and generally aren't infectious.

Instead, transcriptional activation — triggered by exposure to exogenous viruses or other events — leads to expression of viral particles or proteins, such as the HERV-W envelope protein that is involved in MS. Perron's group showed that the protein was expressed in MS patients but not healthy controls, and when administered to animals, produced neurotoxicity with both neuroinflammatory and demyelinating components.

"For 20 years, there was a lot of skepticism around the concept that endogenous retroviruses could play a role in MS pathology," said Perron. "There were a lot of different hypotheses about infectious agents triggering the disease that were never really established. But today, we have a promising therapeutic in the clinic targeting one of the endogenous retroviral antigens."

> "Some viral material could be bad, but most of it is neutral. It doesn't look like it is doing anything, but there are exceptions — those needles in the haystack."
>
> Cedric Feschotte, University of Utah

The company's lead compound is GNbAC1, a humanized IgG4 antibody targeting pathological envelope proteins from HERV-W family member viruses including MSRV, that is in Phase II testing. GNbAC1 is also in Phase I testing for a related indication, chronic inflammatory demyelinating neuropathy (CIDP). Last December, GeNeuro granted Servier an option to license worldwide rights, excluding the U.S. and Japan, to GNbAC1 to treat MS.

While GNbAC1 is GeNeuro's only clinical compound, the company is hoping the results will provide proof of concept that targeting endogenous viruses can have therapeutic effects. Until then, GeNeuro is holding off on investing heavily in the newer indications.

However, it has made forays into schizophrenia and Type I diabetes with two preclinical programs and is starting to set its sights on more indications based on its own research as well as data from its academic collaborators.

"In the field of HERVs, it's not just about HERV-W anymore, and it's not just about MS," Perron told BioCentury. "The endogenous viruses that we once thought were always epigenetically silenced and just a part of the human junk DNA may be activated and contributing to pathology in many different settings."

LINKING ACADEMICS

GeNeuro convened the Lyon meeting — the first of its kind — not only to develop its academic connections but also to promote collaboration among key opinion leaders in HERV.

The biotech is the only company developing therapeutics targeting HERV-W and thinks bolstering the field can advance both the science and its own interests.

"This conference adds credibility to the whole field and to the fact that this body of science is rapidly growing," Perron told BioCentury. "We have people presenting analogous findings and potential new applications in other diseases with other endogenous retroviral families."

He added: "The number of diseases implicating HERVs is growing, and we cannot have in-house specialties for all

DISEASE INDICATIONS INVOLVING HERVs

The table includes selected academic groups studying the effects of human endogenous retroviruses (HERVs) on various diseases. There are several different families of HERVs, including the HERV-H, HERV-K and HERV-W families implicated in diseases, and there are many different viruses within each family. The table lists the family being studied by each group. Groups included in the table presented data on the listed disease indications at the HERVs & Disease workshop in Lyon, France last month.

INDICATION	COMPANY/INSTITUTION	INVESTIGATOR	TARGET	RESEARCH DESCRIPTION
Amyotrophic lateral sclerosis (ALS)	**National Institutes of Health** (NIH)	Avindra Nath	HERV-K	The role of HERVs in ALS and the impact of antiretroviral drugs on ALS pathology.
Autism	**University of Rome** and the **National Institute of Health** (ISS)	Chiara Cipriani; Emanuela Balestrieri	Multiple HERVs	Changes in transcription of various HERVs throughout human lifetimes and the role of HERVs in models of autism.
Cancer	**bioMerieux S.A.** (Euronext:BIM)	François Mallet	HERV-H	Impact of HERV-H expression on gene regulation in colon cancers.
	University Clinic Erlangen	Reiner Strick	Multiple HERVs	Expression of endogenous retrovirus from different HERV families, including HERV-W and HERV-K in human pituitary adenoma and glioblastoma multiforme (GBM).
	University of Rome; **National Research Council of Italy** (CNR)	Claudia Matteucci	HERV-K	HERV-K as a driver of malignant transformation in melanoma.
	Martin Luther University Halle-Wittenberg	Martin Staege	Multiple HERVs	Expression of various HERVs in Hodgkin's lymphoma.
Chronic inflammatory demyelinating polyneuropathy (CIDP)	**University Hospital Henri Mondor**	Alain Créange	HERV-W	HERV-W expression and effects in neurological disorders including CIDPs.
Diabetes	**University of Ulm**	Marion Schneider	HERV-W	Endogenous viral activation and expression of HERV-W in Type II diabetes patient dendritic cells.
	GeNeuro S.A.	Julie Medina	HERV-W	HERV-W envelope and gag proteins expression in Type I diabetes patients.
HIV / AIDS	**University of Sassari**	Antonina Dolei	HERV-W	HERV-W activation in the brains of HIV/AIDS patients and its role in neurological symptoms of the disease.
Multiple sclerosis (MS)	**University of Düsseldorf**	Patrick Küry	HERV-W	The impact of HERV-W on demyelination and how blocking HERV-W envelope promotes remyelination.
	U823 INSERM-University of Grenoble	Patrice Marche	HERV-W	Inflammatory response of endothelial cells to the HERV-W envelope in MS.
	University of Sassari	Antonina Dolei	HERV-W	HERV-W transcriptional activation by exogenous viral infections as a link between infections and MS.
	VU University Amsterdam	Jack van Horssen	HERV-W	HERV-W envelope and gag protein expression in cells in MS lesions.
	University of Utah	John Kriesel	HERV	Expression of HERVs in MS patient brains.
	Cleveland Clinic	Ranjan Dutta	HERV	Expression of HERVs in progressive MS.
	University of São Paulo	Guilherme Sciascia do Olival	HERV-W	Effect of marketed MS therapeutics on HERV-W expression.
Psychosis	**Assistance Publique-Hôpitaux de Paris** (APHP) and **University of Créteil**	Norah Hamdani	HERV-W	HERV-W expression in inflammatory psychoses.
Schizophrenia	**Karolinska Institute**	Hakan Karlsson	HERV-W	HERV-W involvement in schizophrenia onset and pathology.

> "It has been known that exposure to certain viral pathogens predisposes patients to diseases including MS. What hasn't been known is the mechanism linking infection to secondary disease. Transactivation of HERVs could be that link."
>
> Hervé Perron, GeNeuro S.A.

existing diseases, so we always partner with academic groups to investigate new prospects."

At the meeting, presenters provided evidence that the viruses contribute to the pathology of neurological diseases, cancer and diabetes. (See "Disease Indications Involving HERVs", page 10)

For example, several teams showed the HERV-W envelope protein is present in patients with schizophrenia, inflammatory psychosis and Types I and II diabetes. Other groups reported HERV-K family viral elements upregulated in patients with ALS and certain cancers, and HERV-H family elements expressed in colorectal cancers. Although most details of the results presented were not available for disclosure at the time of publication, GeNeuro will make the abstracts available later this month.

Perron wants to use the information as a springboard for launching internal programs.

"Once a role for HERV is confirmed, eliminated, or determined to be involved in a subtype of a diseases, once we have a clear idea of where we can go in that indication, then it is up to an internal discussion to see if and how we should pursue the indication and what the development strategy should be," he said.

Perron told BioCentury that GeNeuro's GNbAC1 MS antibody could be repurposed for new indications involving the HERV-W envelope protein, but the company also has other neutralizing antibodies against that protein that could be optimized for specific indications involving it.

The Lyon meeting also provided data that built on the role of HERV in MS.

GeNeuro and collaborators from the University of Sassari separately presented data implicating HERV-W activation in cases where previous exposure to certain viral infections, such as Epstein-Barr virus (EBV), predisposes patients to MS.

"It has been known that exposure to certain viral pathogens predisposes patients to diseases including MS," Perron said at the meeting. "What hasn't been known is the mechanism linking infection to secondary disease. Transactivation of HERVs could be that link."

Researchers from GeNeuro and the University of Sassari both found that the exogenous viruses cause transactivation of the normally silenced HERV-W virus in the human genome, which leads to expression of the HERV-W envelope protein.

GeNeuro researchers also showed that the HERV-W envelope protein acts as a direct agonist of TLR4, leading to an inflammatory disease phenotype, and that GNbAC1 blocks MSRV envelope binding to TLR4.

Perron told BioCentury that new ideas about how HERVs are involved in disease are beginning to percolate.

For example, he said, the HERV envelope protein acts as a toxin and, while neutralizing this toxin is a priority and defines the major therapeutic issue that is now addressed with GeNeuro's first antibody, combining therapeutics against the envelope toxin with agents that prevent viral activation could be more effective.

GeNeuro is having internal discussions about creating additional molecules for combination therapy in MS and has patents covering therapeutic combinations, but development of the lead antibody takes priority at this time.

"These diseases we're going after are complex," he said. "For MS, we're targeting the toxin that has downstream pro-

inflammatory and neurotoxic effects, but there may be future ways to complement this treatment and make it more effective."

Perron drew an analogy with treatment of tetanus using toxin antiserum combined with antibiotics, and said that combining therapeutics against the envelope toxin with agents that prevent viral activation in the first place could potentiate the antibody's activity.

SEEKING COMPANIONS

While GeNeuro is keeping its focus on academia for early stage programs, the company is looking to partner with industry for later-stage programs, in particular to help it conduct large-scale clinical trials.

"We have just announced our partnership with Servier in Europe for the MS indication, but we are still open to others. For example, the American region is still open," said Perron.

In addition, he said the company will pursue companion diagnostics, to determine the level of the endogenous retrovirus envelope protein immunotoxin in a patient and help select patients for treatment.

GeNeuro gained rights to the IP on diagnostics for HERV-W proteins from bioMerieux last year, to allow parallel development with its therapeutics. "We need to be able to innovate within our specialized company even when it comes to diagnostics," said Perron. "When looking at HERVs, we are not dealing with the classical issues."

GeNeuro also has filed IP covering HERV-W in various diseases, and covering the use of different types of molecules to target HERV-W antigens. The company is restricting its pipeline and IP to therapeutics targeting HERV-W family viral proteins, but is exploring the role of other HERV families, including HERV-K, through academic partnerships. 7

COMPANIES AND INSTITUTIONS MENTIONED

bioMerieux S.A. (Euronext:BIM), Marcy l'Etoile, France
GeNeuro S.A., Geneva, Switzerland
Servier, Neuilly-sur-Seine, France
University of Sassari, Sassari, Italy
University of Utah, Salt Lake City, Utah

TARGETS AND COMPOUNDS

IgG4 - Immunoglobulin G4
MSRV - Multiple sclerosis-associated human endogenous retrovirus
TLR4 - Toll-like receptor 4

REFERENCES

Cukier-Meisner, E. "Verve for HERV." *BioCentury* **(2014)**