Archamps (France), March 3, 2020 at 6:00 pm CET

Genkyotex's setanaxib significantly improves immunotherapy including checkpoint inhibitors in multiple preclinical cancer models

- ***Study showing that setanaxib breaks treatment resistance to checkpoint inhibitors was published in Cancer Research, the journal of the American Association for Cancer Research***
- ***Data suggest the possibility of using setanaxib in combination with multiple types of immunotherapies to enhance treatment responses***
- ***Multiple publications with setanaxib and other Genkyotex molecules highlight the strong interest for NOX therapies and Genkyotex compounds***

Genkyotex (Euronext Paris & Brussels: FR0013399474 – GKTX), a biopharmaceutical company and the leader in NOX therapies, announced today that setanaxib, the Company's NOX1 and NOX4 inhibitor, was shown to significantly improve immunotherapy in multiple preclinical cancer models. Results from this preclinical study were published in Cancer Research, a peer-reviewed journal of the American Association for Cancer Research.

In this study, conducted by Professor Gareth Thomas and his colleagues at the University of Southampton, United Kingdom, setanaxib was able to overcome immune cell exclusion and enhance response to multiple immunotherapies. Immune exclusion, the inability of effector T-cells to penetrate the tumor and kill cancer cells, is emerging as one of the key causes of resistance to immunotherapies such as checkpoint inhibitors, adoptive T-cell therapy, and therapeutic vaccines. This study showed that the exclusion effect is caused by activated cancer associated fibroblasts (CAFs), making CAFs a promising therapeutic target, but as yet, there are no clinically available CAF-specific inhibitors.

The Southampton team had previously identified the enzyme NOX4 as a key regulator of CAF activation in multiple solid cancers. In the present study, they tested the effect of setanaxib, Genkyotex's NOX1 and NOX4 inhibitor, and found that it reverses CAF activation, overcomes immune exclusion and promotes infiltration of $CD8^+$ T-cells into tumors. Importantly, setanaxib abolished treatment resistance and enhanced immunotherapeutic responses to anti-PD1 antibodies and therapeutic vaccination.

This work is supported by a Small Molecule Drug Discovery grant from Cancer Research UK (CRUK) to evaluate the optimal clinical development strategy for setanaxib in oncology. Cancer Research UK is the world's leading cancer charity dedicated to saving lives through research. The objective of the funded program is to inform the design of a potential clinical trial of setanaxib in combination with an available immunotherapy.

"Immunotherapy has been the most important advance in cancer treatment for several decades, and overcoming the tumor immune exclusion effect is now a major goal, since it significantly limits its effectiveness. These new results provide evidence that setanaxib improves immunotherapy response in CAF-rich tumors, and this could help a significant proportion of patients who are currently resistant to this type of treatment" **said Professor Gareth Thomas.**

"These results are consistent with setanaxib's anti-fibrotic mechanism and suggest that setanaxib could become an important adjunctive therapy used in combination with several types of immunotherapies. Clinical proof of concept for its anti-fibrotic effect and favorable safety profile has been demonstrated in our recent trial in liver fibrosis. These results pave the way for the clinical evaluation of setanaxib in oncology" **said Philippe Wiesel, M.D., Executive Vice President and Chief Medical Officer of Genkyotex.**

The original research article, entitled **"NOX4 inhibition potentiates immunotherapy by overcoming cancer-associated fibroblast-mediated CD8 T-cell exclusion from tumors"** is currently available on the website of Cancer Research.

Other publications

Multiple publications over the last year highlight the strong interest for NOX therapies. A selection of manuscripts published in the second half of 2019 and the first quarter of 2020 is listed below:

1. Nox (NADPH Oxidase) 1, Nox4, and Nox5 Promote Vascular Permeability and Neovascularization in Retinopathy. Deliyanti D, Alrashdi SF, Touyz RM, Kennedy CR, Jha JC, Cooper ME, Jandeleit-Dahm KA, Wilkinson-Berka JL. Hypertension. 2020 Mar 2: Hypertension. AHA11914100. doi: 10.1161
2. A closer look into NADPH oxidase inhibitors: Validation and insight into their mechanism of action. Reis J, Massari M, Marchese S, Ceccon M, Aalbers FS, Corana F, Valente S, Mai A, Magnani F, Mattevi A. Redox Biol. 2020 Feb 15;32:101466. doi: 10.1016/j.redox.2020.101466. [Epub ahead of print]
3. Targeting the NADPH Oxidase-4 and Liver X Receptor Signaling Axis Preserve Schwann Cell Integrity in Diabetic Mice. Eid SA, El Massry M, Hichor M, Haddad M, Grenier J, Dia B, Barakat R, Boutary S, Chanal J, Aractingi S, Wiesel P, Szyndralewiez C, Azar ST, Boitard C, Zaatari G, Eid AA, Massaad C. Diabetes. 2019 Dec 27
4. Isoform-selective NADPH oxidase inhibitor panel for pharmacological target validation. Dao VT, Elbatreek MH, Altenhöfer S, Casas AI, Pachado MP, Neullens CT, Knaus UG, Schmidt HHHW. Free Radic Biol Med. 2020 Feb 20;148:60-69. doi: 10.1016/j.freeradbiomed.2019.12.038. Epub 2019 Dec 25.
5. A physician-initiated double-blind, randomised, placebo-controlled, phase 2 study evaluating the efficacy and safety of inhibition of NADPH oxidase with the first-in-class Nox-1/4 inhibitor, GKT137831, in adults with type 1 diabetes and persistently elevated urinary albumin excretion: protocol and statistical considerations. Reutens AT, Jandeleit-Dahm K, Thomas M, Bach LA, Colman PG, Davis TME, D'Emden M, Ekinci EI, Fulcher G, Hamblin PS, Kotowicz MA, MacIsaac RJ, Morbey C, Simmons D, Soldatos G, Wittert G, Wu T, Cooper ME, Shaw JE. Contemp Clin Trials. 2019 Nov 15:105892
6. Spironolactone suppresses aldosterone-induced Kv1.5 expression by attenuating mineralocorticoid receptor-Nox1/2/4-mediated ROS generation in neonatal rat atrial myocytes. Lu G, Li J, Zhai Y, Li Q, Xie D, Zhang J, Xiao Y, Gao X. Biochem Biophys Res Commun. 2019 Dec 3;520(2):379-384.
7. Nox2 and Nox4 Participate in ROS-Induced Neuronal Apoptosis and Brain Injury During Ischemia-Reperfusion in Rats. Wang J, Liu Y, Shen H, Li H, Wang Z, Chen G. Acta Neurochir Suppl. 2020;127:47-54
8. Activated hepatic stellate cells and portal fibroblasts contribute to cholestatic liver fibrosis in MDR2 knockout mice. Nishio T, Hu R, Koyama Y, Liang S, Rosenthal SB, Yamamoto G, Karin D, Baglieri J, Ma HY, Xu J, Liu X, Dhar D, Iwaisako K, Taura K, Brenner DA, Kisseleva T. J Hepatol. 2019 Sep;71(3):573-585
9. NADPH oxidase 4 mediates TGF-β1/Smad signaling pathway induced acute kidney injury in hypoxia. Cho S, Yu SL, Kang J, Jeong BY, Lee HY, Park CG, Yu YB, Jin DC, Hwang WM, Yun SR, Song HS, Park MH, Yoon SH. PLoS One. 2019 Jul 18;14(7)
10. Acute Changes in NADPH Oxidase 4 in Early Post-Traumatic Osteoarthritis. Wegner AM, Campos NR, Robbins MA, Haddad AF, Cunningham HC, Yik JHN, Christiansen BA, Haudenschild DR. J Orthop Res. 2019 Jul 15

11. Pharmacological characterization of the seven human NOX isoforms and their inhibitors. Augsburger F, Filippova A, Rasti D, Seredenina T, Lam M, Maghzal G, Mahiout Z, Jansen-Dürr P, Knaus UG, Doroshow J, Stocker R, Krause KH, Jaquet V. Redox Biol. 2019 Sep;26:101272. doi: 10.1016/j.redox.2019.101272.

About Cancer Research

Cancer Research is a peer-reviewed scientific journal published by the American Association for Cancer Research. It covers research on all aspects of cancer and cancer-related biomedical sciences and was established in 1941. Its impact factor is 8.4.

About Genkyotex

Genkyotex is the leading biopharmaceutical company in NOX therapies, listed on the Euronext Paris and Euronext Brussels markets. Its unique platform enables the identification of orally available small-molecules which selectively inhibit specific NOX enzymes that amplify multiple disease processes such as fibrosis, inflammation, pain processing, cancer development, and neurodegeneration. Genkyotex is developing a pipeline of first-in-class product candidates targeting one or multiple NOX enzymes. The lead product candidate, setanaxib (GKT831), a NOX1 and NOX4 inhibitor has shown evidence of anti-fibrotic activity in a Phase II clinical trial in primary biliary cholangitis (PBC, a fibrotic orphan disease). Based on its positive Phase II results, a phase 3 trial with setanaxib in PBC is being planned. Setanaxib is also being evaluated in an investigator-initiated Phase II clinical trial in Type 1 Diabetes and Kidney Disease (DKD). A grant from the United States National Institutes of Health (NIH) of $8.9 million was awarded to Professor Victor Thannickal at the University of Alabama at Birmingham (UAB) to fund a multi-year research program evaluating the role of NOX enzymes in idiopathic pulmonary fibrosis (IPF), a chronic lung disease that results in fibrosis of the lungs. The core component of this program is a Phase 2 trial with setanaxib in patients with IPF scheduled to recruit patients in first semester of 2020. This product candidate may also be active in other fibrotic indications.

Genkyotex also has a versatile platform well-suited to the development of various immunotherapies (Vaxiclase). A partnership covering the use of Vaxiclase as an antigen per se (GTL003) has been established with Serum Institute of India Private Ltd (Serum Institute), the world's largest producer of vaccine doses, for the development by Serum Institute of cellular multivalent combination vaccines against a variety of infectious diseases.

For further information, please go to *www.genkyotex.com*

GKTX
LISTED
EURONEXT

ELIGIBLE
PEA
PME

CONTACTS

GENKYOTEX
Alexandre Grassin
CFO
Tel.: +33 (0)5 61 28 70 60
investors@genkyotex.com

NewCap
Dušan Orešanský
Tel.: +33 1 44 71 94 92
genkyotex@newcap.eu

Disclaimer

This press release may contain forward-looking statements by the company with respect to its objectives. Such statements are based upon the current beliefs, estimates and expectations of Genkyotex's management and are subject to risks and uncertainties such as the company's ability to implement its chosen strategy, customer market

trends, changes in technologies and in the company's competitive environment, changes in regulations, clinical or industrial risks and all risks linked to the company's growth. These factors as well as other risks and uncertainties may prevent the company from achieving the objectives outlined in the press release and actual results may differ from those set forth in the forward-looking statements, due to various factors. Without being exhaustive, such factors include uncertainties involved in the development of Genkyotex's products, which may not succeed, or in the delivery of Genkyotex's products marketing authorizations by the relevant regulatory authorities and, in general, any factor that could affects Genkyotex's capacity to commercialize the products it develops. No guarantee is given on forward-looking statements which are subject to a number of risks, notably those described in the universal registration document filed with the AMF on January 16, 2020 under number 20-0012, and those linked to changes in economic conditions, the financial markets, or the markets on which Genkyotex is present. Genkyotex products are currently used for clinical trials only and are not otherwise available for distribution or sale.