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N4 Pharma / EpiVax

Final Consulting Report

Independent Appraisal of Nuvec Platform

Confidential Report Developed For:
Nigel Theobald
Founder & CEO
N4 Pharma Plc
Weston House, Bradgate Park View
Chellaston, Derby DE73 5UJ, United Kingdom
nigel@n4pharma.co.uk

Prepared By:
Amy S. Rosenberg, M.D., Consultant and
Riley Nolan, Business Development Associate
EpiVax, Inc.
188 Valley Street, Suite 424
Providence, RI 02909
E: arosenberg@epivax.com

Pursuant to recent consulting discussions, the following final consulting report contains Dr. Amy Rosenberg's independent appraisal of N4 Pharma's Nuvec® platform. The N4 Pharma team requested an independent appraisal to focus on potential regulatory/clinical use of the intra-tumour delivery of N4's multi siRNA loaded nanoparticles. Dr. Amy Rosenberg is uniquely suited to appraise the Nuvec® platform, as she has deep expertise in immunogenicity and immune tolerance and extensive knowledge of regulatory processes from her 30+ years with the US FDA. Dr. Rosenberg offers consulting services through EpiVax, Inc.'s Trusted Expert Advice (TEA) consulting service, under which this work was carried out.

Background:
In spite of the success of diverse approaches to treatment of cancer, the critical shortcomings of such approaches demand the need for novel, innovative strategies that neither have the toxicity of broad stroked chemotherapy, the limitations of monoclonal antibodies to growth factor receptors expressed on tumors, nor the limited efficacy of immunotherapy.

While remarkably successful for some cancers, immunotherapeutic approaches to treatment of cancer have thus far failed to affect progression of numerous cancers (1-3) especially those with low mutational burden, such as pancreatic cancer. Moreover, even for tumors with higher mutational burdens, checkpoint inhibitory mAbs (CPI) may fail to fully activate T and other effector cells due to their diminished numbers and capacity from prior treatments with chemo and radiotherapies, as immunotherapies have historically been given as second or later line treatments (4). Increasingly however, CPI treatments are being given as first line therapies in acknowledgment of the importance of an intact immune system for optimal results (5). Crucially, the post-treatment emergence of cancer cells that have developed "immune escape" pathways including loss of target antigens, often renders retreatment with check point inhibitors futile (6,7). Furthermore, treatment emergent severe adverse events often accompany immunotherapy including development of autoimmune disease that may require immune suppression, most unwanted in the context of tumor immunotherapy (8-10).

Thus, novel approaches to treatment of cancer that do not rely on the immune response, nor incur the general toxicity induced by chemo or radiotherapy (11,12), but rather rely on targeting the well-known growth factor pathways spurring tumor growth are key to addressing the shortfalls of immunotherapeutic and chemotherapeutic approaches. Although some monoclonal antibodies (mAbs) are approved to treat malignancies by targeting tumor growth dependent pathways, most prominently mAbs to Epidermal Growth Factor Receptor (13), they have highly significant off target effects (14,15), must be given repetitively, can be immunogenic, and are associated with the inevitable emergence of treatment resistant tumor populations (16,17). None have been curative. N4 Pharma has developed a novel approach which may overcome the limitations outlined above.

Appraisal of N4 Pharma's Nuvec® Platform:
To address current shortcomings in cancer therapy, N4 Pharma has developed a breakthrough silica nanoparticle delivery system to safely and efficiently deliver small interfering RNAs (siRNAs) to tumors thereby inhibiting multiple tumor growth factor pathways, leading to tumor cell death (18,19).

Critically, N4 Pharma's Nuvec® particles have a unique irregular surface structure that effectively traps and protects the siRNA (or RNA/DNA payload) as it migrates into the cancer cells. Nuvec® can bind multiple siRNAs in its filamentous structure, thereby better ensuring that tumors will not escape one growth factor pathway to again proliferate by the emergence of an alternative growth pathway.

Due to its potential to deliver multiple siRNAs, the Nuvec® delivery system improves on other particle delivery systems which can only be loaded with one siRNA at a time. An additional advantage of Nuvec® is that it can be engineered to display ligands for specific tumour types. This will potentially enhance tumor killing by targeting the delivery of the siRNA to the tumor and may improve the clinical response with fewer adverse events when compared to mAbs to tumor growth factors, checkpoint inhibitor immunotherapy and conventional chemotherapy. Moreover, unlike cytokine therapies directed into tumors, from which there may be dissemination from the tumor into the tumor microenvironment and systemically (20), the retention of Nuvec® particles within tumor cells is expected to reduce systemic exposure.

An additional critical advantage of siRNA therapeutics over alternatives such as growth factor-targeting mAbs and checkpoint inhibitor immunotherapies is that although siRNAs can promote an innate immune response, they are not known to induce anti-drug antibodies. By way of contrast mAb-based approaches are known to induce anti-drug antibodies which may limit the efficacy of repeated doses (21). The ability to deliver repeated doses of Nuvec bound siRNAs without the induction of interfering anti-drug antibodies gives Nuvec a significant advantage over mAb-based approaches. In addition the reduced immunogenic profile of the Nuvec system may limit potential adverse events associated with the inflammatory or immune response.

N4Pharma is looking to move toward clinical studies by performing preclinical toxicology studies in relevant in vitro and animal models, assessing activity on different tumor types, defining the optimal route of administration and further examining the benefits of blocking multiple growth factor pathways rather than just one pathway.

Thank you for the pleasure of providing N4 Pharma with our consulting support services. Please feel free to contact us with any questions you may have or if you would like to discuss these findings in more detail.

Sincerely,

Amy S. Rosenberg, M.D., Consultant
EpiVax, Inc.

Consultant Background:
Amy Rosenberg, M.D. holds over 30 years of experience in the immunogenicity field, most notably as the Director of the Division of Therapeutic Proteins, subsequently Division 3 in the Office of Biotechnology Products at the FDA. While at the FDA, Dr. Rosenberg oversaw the regulation and approval of many protein therapies, stem cell selection devices, monoclonal antibodies and fusion proteins, enzyme replacement therapies, immunomodulators, hematologic and somatic cell growth factors, and combination devices-biologics.

Dr. Rosenberg was also a principal author of the 2014 FDA guidance titled ***"Immunogenicity Assessment for Therapeutic Protein Products"*** and served as expert consultant to the National Institute of Health's Immune Tolerance Network as well as to the European ABIRISK consortium. In 2021, Dr. Rosenberg joined EpiVax as Senior Director of Immunology & Protein Therapeutics and offers her expertise to pharmaceutical scientists in the areas of pre-clinical, IND-stage, and clinical immunogenicity risk strategy.

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