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\Orchestrating a brighter world

NEC

NEC: harnessing artificial intelligence-powered drug development to provide tailored medicines

Individualized cancer therapies represent the next step for cancer immunotherapy. NEC Corporation has developed cutting-edge artificial intelligence to predict patient-specific neoantigens to turn this promise into reality and extend the approach to infectious diseases.

For more than 120 years, NEC Corporation has been at the forefront of information and communication technology. It is now steadily perfecting its artificial intelligence (AI) technologies stretching back decades to rapidly address complex social issues. NEC's AI-driven solutions are presently used in multiple facets of society: immigration control systems equipped with the world's most accurate facial-recognition technology; retail supply forecasting to minimize losses; and medical devices for early detection of disease. The company is now bringing this accumulated expertise to bear on the challenge of developing truly individualized therapies for patients with cancer—part of NEC's broader mission to orchestrate a brighter world.

NEC's move into biopharma reflects the company's dedication to creating social values that promote health and well-being for all. NEC updated its articles of incorporation in 2019 to propel its ambition of creating transformative medicines, looking beyond purely providing services to the pharma industry.

Along with other healthcare initiatives at NEC, the AI Drug Development Division (AIDD) is working towards this mission through the AI-guided design and development of individualized neoantigen vaccines. One of these is currently in clinical trials for two solid tumors, and another is poised to enter human trials in the near future, making NEC the first Japanese company to run clinical trials in this therapeutic space.

NEC's entry into the cancer vaccine development arena is the result of decades of work on cancer research with academic institutions, as well as numerous partnerships created to build its oncology pipeline. In 2019, NEC acquired the Norwegian bioinformatics company OncoImmunity, a recognized player in the neoantigen prediction field. NEC has since developed a more advanced AI system, called the NEC Immune Profiler, which leverages the scientific strengths and technologies of both companies. The AIDD team, based in Japan, forms part of a larger distributed virtual organization comprising global talents from NEC Labs America, NEC Labs Europe, NEC India, and NEC OncoImmunity. This life science innovation hub brings together experts in a range of disciplines, from biology to data science, to fulfil AIDD's goal of creating new, AI-guided precision medicines to improve the quality of life of patients around the world.

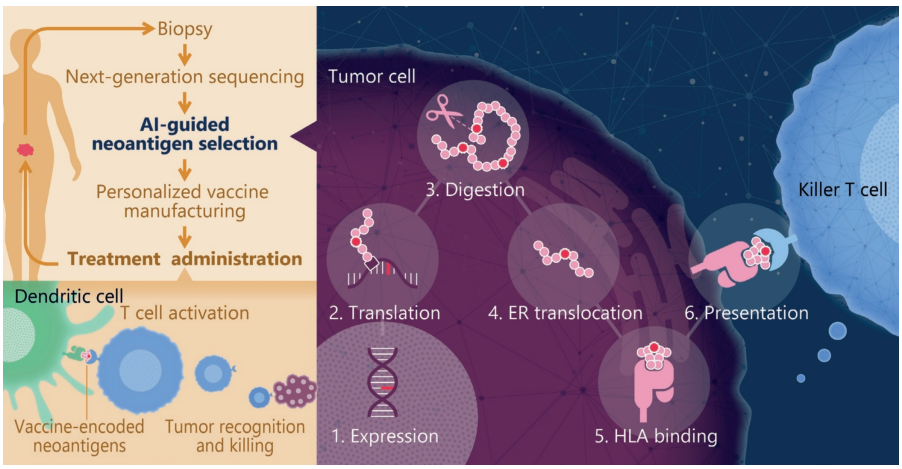

Fig. 1 | NEC's holistic approach to identifying neoantigens. The NEC Immune Profiler models every step in antigen processing (right) to identify neoantigens that feed into the process of developing and delivering an individualized therapy to the patient (left). ER, endoplasmic reticulum; HLA, human leukocyte antigen.

The promise of individualized vaccines

Cancer immunotherapy—engaging the body's own immune system in the fight against cancer—has emerged in recent decades as a powerful fourth pillar of cancer treatment, along with conventional chemotherapy, radiation therapy and surgery. One of the most important developments in cancer therapy in the past ten years has been the launch of checkpoint inhibitors, which show impressive results—but only in some patients, owing to the genetic heterogeneity of cancer and the immune system.

Many previous cancer vaccines were directed against tumor-associated antigens (TAAs)—self-antigens that are abnormally or overexpressed in tumors—but these targets have two major drawbacks. First, because TAAs are self-antigens, there is often central or peripheral T cell tolerance to these proteins, so TAA-directed cancer vaccines often fail to elicit clinically effective antitumor immune responses. Second, because TAAs are often expressed, even if at low levels, in healthy tissue as well as tumors, they also have the propensity to create collateral damage by killing healthy cells, leading to systemic toxicity.

A promising alternative to targeting TAAs is to develop vaccines against cancer neoantigens. These are de novo altered self-peptides created by specific mutations in a patient's tumor, and are not expressed in healthy tissues. This means that neoantigens are not subject to the problems of tolerance and toxicity associated with TAAs. As neoantigen-based vaccines are based on mutations unique to every patient, they represent a truly individualized therapy that can generate long-lasting T cell-based immunity that not only destroys existing tumors but might offer protection against disease recurrence.

Historically, identifying patient-specific neoantigens has been costly, time-consuming and technically challenging. Today, the availability of next-generation sequencing, combined with massive computing power and advanced AI, has created a confluence of trends that NEC, with decades of experience in both AI and life-science research, is well positioned to put to work in developing individualized neoantigen vaccines. Although the scientific and computational challenges involved in neoantigen prediction are considerable, NEC's AIDD is showing the way forward.

Best-in-class neoantigen prediction

Predicting neoantigens is like finding a specific needle in a large pile of needles. Cancerous cells accumulate thousands of unique mutations, but only 1–2% result in peptide sequences that can be recognized by the patient's immune system—these are true immunogenic neoantigens. For a mutated peptide to elicit an immune response, specifically a T cell-mediated response, it must be recognized by a T cell receptor (TCR). TCRs, however, do not recognize naked peptides; instead,

they recognize peptides bound to human leukocyte antigen (HLA) proteins that are expressed on the cell surface. So neoantigen prediction has to look beyond the peptide itself and take into account the genetic HLA background of each patient.

As a result, much work in this area has focused on predicting whether a potential neoantigen will bind different allelic variants of HLA. While this is a crucial component of neoantigen prediction, it has usually been pursued to the neglect of many other biological processes that affect whether a mutated protein is a bona fide neoantigen. These include the initial transcription and expression of mutated genes through translation, post-translational modification and proteosomal processing, translocation to the endoplasmic reticulum, intracellular binding of neoantigen to HLA proteins, and, finally, presentation of the neoantigen–HLA complex at the cell surface.

The NEC Immune Profiler, which is the company's cutting-edge neoantigen prediction system, takes a holistic approach to this problem, combining transcriptomic, proteomic and other data to model all the steps in this process to identify truly immunogenic neoantigens (Fig. 1). It is unique in predicting with high accuracy whether a putative neoantigen will actually be presented in an HLA complex at the tumor cell surface, without which it will not generate an anticancer immune response. NEC's machine-learning models are informed by proprietary data on peptides and their neoantigenic properties created in academic and commercial partnerships, as well as publicly available datasets. It uses these data to build a powerful AI system that integrates multiple patent-pending tools, including novel deep learning and graph-based approaches developed by the NEC group.

This integrated approach, and the ability to identify neoantigens that will be presented at the cell surface, has been extensively validated using retrospective oncology data and data from proprietary peptide elution studies. For example, against a sample of 10,000 randomly generated peptides from the human proteome, conventional HLA binding-focused approaches identified just 20% of true hits in the top 10 ranked candidates—that is, peptides that would be presented at the cell surface and elicit an immune response—whereas NEC's AI predicted 80% of true hits.

To date, this neoantigen prediction technology has been deployed to generate individualized cancer-vaccine candidates for clinical testing. In October 2018, NEC announced a collaboration with French biotechnology company Transgene to develop vaccines for solid cancers that combine neoantigens identified by NEC's AI with Transgene's myvac gene-delivery platform—a proprietary system built around modified vaccinia Ankara (MVA) virus that has a proven clinical safety track record and is known for its efficient immunogenicity in patients. In January 2020, NEC and Transgene launched two phase 1 trials of their first jointly developed product, TG4050, one in head and neck cancer, and the other in ovarian cancer. TG4050 is designed to carry multiple patient-specific neoantigens with each individualized batch manufactured. Initial data from these trials has shown that TG4050 delivered as a monotherapy is well tolerated and induces robust antitumor cellular immune responses against multiple neoantigen targets.

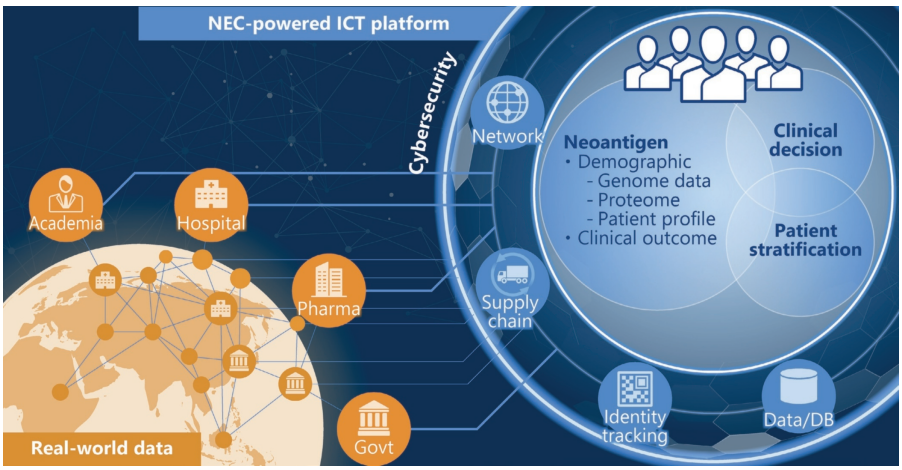

Fig. 2 | NEC's vision for the future. NEC's envisioned ICT (information and communication technology) platform will orchestrate a secure and reliable exchange of healthcare data between various stakeholders around the world to ensure that personalized treatments are delivered to patients.

NEC's other individualized neoantigen cancer-vaccine candidate, NECVAX NEO1, was developed under a strategic collaboration established in 2019 with Swiss–German biotech VAXIMM. It uses VAXIMM's orally administered, bacteria-based vaccine platform to deliver NEC-identified neoantigens. In March 2022, NEC OncoImmunity acquired all of VAXIMM's neoantigen-related development assets, and NECVAX NEO1 is poised to move from preclinical development to clinical trials in the near future, with NEC OncoImmunity as trial sponsor.

Beyond cancer

The COVID pandemic in 2020 created a new opportunity to apply NEC's AI-enabled antigen prediction technology to help solve an urgent medical and social need. Instead of comparing DNA sequences from healthy and cancerous tissue, the AI looked into sequences of thousands of SARS-CoV-2 variants to pinpoint 'immunogenic hotspots'—regions unusually rich in T cell epitopes—which are able to bind and be presented on the surface of infected cells by most HLA variants in the global population.

The spike protein is the primary target for generating protective antibody responses in the current COVID vaccines. However, because the spike protein mutates frequently, it is highly likely that new vaccines will have to be developed in the future to deal with immune escape variants. NEC's T cell-centric approach looks beyond the spike, and builds blueprints that include overlapping epitopes from more-conserved regions of the virus, which are capable of eliciting broader T cell immunity that is more resistant to the emergence of immune escape variants and may eliminate the need for new vaccines.

A crucial difference between individualized cancer vaccines and a broadly protective infectious-disease vaccine is that, in the former, antigens are HLA-matched to the patients, whereas the latter must take into account global HLA diversity to ensure that selected antigens have the greatest likelihood of generating an immune response when applied at a population level. NEC adopted a vaccine-optimization approach, in which a set of data-driven hierarchical Bayesian models create digital twins that model the HLA diversity of a target population. This elaborate simulation allows for the careful and rapid selection of an optimal combination of antigens that will cover and protect the vast majority of the population. NEC is keen on extending its research to the global challenge of combating infectious diseases.

The future of individualized therapies

The creation and delivery of individualized therapies requires the integration of highly sensitive patient data from multiple, distributed sources such as hospitals, CMOs and government institutions. Protecting patient data requires robust, secure data-handling systems that ensure a reliable 'chain of identity' (the transparent and permanent association of patients with their samples, data, final drug product and post-treatment monitoring), and 'chain of custody' (who processed the samples, data or drug product, and what they did at each stage).

A lack of standardized data formats among the various stakeholders poses another challenge. With different datasets stored in non-compatible formats, data sharing can become difficult and ineffective. This problem is exacerbated by the stringent regulatory requirements for protecting personal data that travels between stakeholders and across national borders.

As a leader in ICT (information and communication technology), NEC aspires to build on its expertise and develop an ICT platform that tackles these challenges by leveraging blockchain and other technologies to enable secure, reliable and efficient data exchange among various stakeholders in healthcare (Fig. 2), with the ultimate goal of achieving cross-functional decision-making for improved patient outcomes.

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