OncoTherapy Science, Inc.
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Working with a genomics pioneer to develop safer, more effective cancer treatments

With the key goal of improving the outcomes for people with cancer, university-launched OncoTherapy Science, Inc. is developing a pipeline of small-molecule drugs and a number of therapeutic peptide vaccines.

OncoTherapy Science, Inc. (OTS) is approaching a big moment in its mission to develop safer, more effective treatments for cancer. Having spent the past 15 years building a pipeline of first-in-class cancer compounds, OTS is now closing in on two sets of clinical proof-of-concept data that will shape the next stage of its history.

The data sets will mark the culmination of decades of research into the genomics of cancer. OTS was founded in 2001 to investigate and develop cancer therapies and vaccines based on research by Professor Yusuke Nakamura, a personalized-medicine pioneer who was the director of the Human Genome Center at the University of Tokyo before he took a post at the University of Chicago. For decades, Nakamura has pushed the use of large-scale genomics research to understand the causes of cancer while simultaneously working toward the discovery of oncology peptide vaccines and targeted drugs.

OTS is a beneficiary of Nakamura's breakthrough research projects. As a university-launched venture company, OTS has enjoyed close ties with Nakamura and his colleagues since it first began operating in Tokyo, Japan, around the time that the Human Genome Project was publishing its working draft. In the intervening years, OTS has positioned itself at the forefront of the movement to turn the work of genomics pioneers into treatments and vaccines that could make a meaningful difference in the lives of people with cancer who have unmet medical needs.

A genomics-driven method of target selection

OTS's focus on the development of effective cancer treatments without the adverse events associated with existing drugs has led it to center its research program on gene products that are common and abundant in tumors but rare or absent in healthy tissues. Other research groups share similar aims. OTS, however, having entered the field early in the history of genomics with the support of Nakamura, has established a process that has enabled it to become the first company to develop small molecules and antibodies to a clutch of cancer-related targets.

The target-identification process is underpinned by laser-microbeam microdissection (LMM), a tool that Nakamura's group uses to separate cancer cells from tumors. By filtering out stromal and other healthy cells found in tumor samples, the group is able to obtain pure populations of cancer cells that can be probed for insights into how they are distinct from the components of normal tissues. Nakamura's group gathers details of these distinguishing characteristics by using an in-house-designed cDNA microarray system with the sensitivity and specificity needed to obtain expression profiles of almost all human genes.

This process leads to the identification of genes that are expressed more in tumor cells than in normal cells, or that are needed in high quantities for cancer to develop. These genes are the starting point in OTS's search for drug targets. To validate the targets, Nakamura's group at the University of Tokyo performs gene knockdown with small interfering RNA (siRNA); immunohistochemistry using specific antibodies; and other techniques, after which it decides whether a small molecule, antibody or peptide vaccine would be the most appropriate medical intervention to advance into development.

The potential of MELK and TOPK inhibitors

OTS has used the outcome of the group's work to generate a pipeline of small-molecule drugs with eight novel targets, the most advanced of which is moving toward clinical proof of concept. The

Pipelines as of Jan. 2016

	Product	Target/disease	Basic research	Lead optimization	Preclinical	Phase 1	Phase 2	Phase 3
Small Molecule	OTS167	MELK (solid tumor) MELK (AML)	→	→	→	→		
	OTS964, etc.	TOPK	→	→	→			
	-	First-in-class; five onco-targets	→	→				
Cancer Peptide Vaccines	S-588410 * (Out-licensing to Shionogi)	Esophageal cancer	→	→	→	→	→	→
	(Out-licensing to Shionogi)	Bladder cancer; head and neck cancer	⇢	⇢	⇢	⇢	⇢	
	(Out-licensing to Ono)	Hepatocellular carcinoma	⇢	⇢	⇢	⇢		
	(Out-licensing to Otsuka)	Colorectal cancer	⇢	⇢	⇢	⇢		
Antibodies	OTSA101	Synovial sarcoma	→	→	→	→		
	(Out-licensing to Kyowa Kirin)	Alzheimer's disease	⇢	⇢	⇢	⇢		

Figure 1: Current pipeline at OncoTherapy Science. Solid lines show the hands-on R&D products (including development assistance for out-licensing S-588410*). Dashed lines show out-licensing products being developed by other companies.

optimized small-molecule candidate OTS167 targets MELK, a serine/threonine protein kinase encoded by *MELK* gene. MELK is overexpressed in cancer stem cells (CSCs) and in hematological cancers as well as in solid tumor. By phosphorylating a handful of substrates, MELK regulates the proliferation and invasion of cancer cells while driving the formation of CSCs and preventing cell death.

In people with acute myeloid leukemia (AML), high levels of *MELK* mRNA expression correlate with poorer outcomes in terms of both overall and event-free survival. Preclinical testing has shown that OTS167 can control tumor progression better than the chemotherapy drug paclitaxel, which suggests that it could improve outcomes in cancers associated with the overexpression of MELK. OTS is now testing this idea in the clinic. A 42-person phase I trial of the intravenous form of OTS167 is under way at the University of Chicago, which sets OTS up to generate data showing that the drug is safe in people with advanced solid tumors.

The development of OTS167 is happening in parallel with that of a pair of first-in-class TOPK (T lymphokine–activated killer cell–originated protein kinase) inhibitors. Similarly to MELK, TOPK is found at high levels in certain cancers, including those that affect the lungs, breasts and bladder. Given that TOPK meets the OTS's criteria, which mandate that it be found in high levels in cancerous cells but remain largely absent from healthy tissues, the company is developing two inhibitors of the target, OTS514 and OTS964. Both molecules potently inhibit TOPK without having a large effect on other kinases.

OTS has demonstrated the therapeutic potential of such inhibition in preclinical testing. When its liposomal formulation was administered intravenously in lung cancer xenograft models, OTS964 caused complete tumor regression without having a negative effect on body weight. The targeted antitumor activity implied by the data is indicative of the R&D strategy in place at OTS, which is focused on maximizing efficacy while eliminating adverse events. This ethos underpins OTS's development of small molecules aimed at six other novel targets, including three histone methyltransferases (HMTs).

Using peptide vaccines to arm the immune system

The small-molecule-drug development program is just one of the ways in which OTS is using the pioneering genomics research performed by Nakamura to improve the care of cancer patients. OTS also has a pipeline of cancer peptide vaccines that are subject to out-licensing deals with Otsuka Pharmaceutical, Ono Pharmaceutical and Shionogi. The most advanced of the six clinical-stage therapeutic vaccines developed by OTS is a phase III product that targets cancer of the esophagus. Each of the vaccine candidates is underpinned by the same scientific concept.

Cancer antigen peptides are the cornerstone of the project. Found on the surface of cancer cells in complexes with human leukocyte antigen (HLA), these antigens are recognized by the immune system as invaders, which triggers a response that leads the body to attempt to kill the offending tumor cells.

When applied to a target that is expressed specifically in tumors and that is essential for the growth and survival of cancerous tissue, such an approach fits perfectly with OTS's mission to treat diseases without harming patients. OTS has data to show the potential of its vaccines to live up to this ideal.

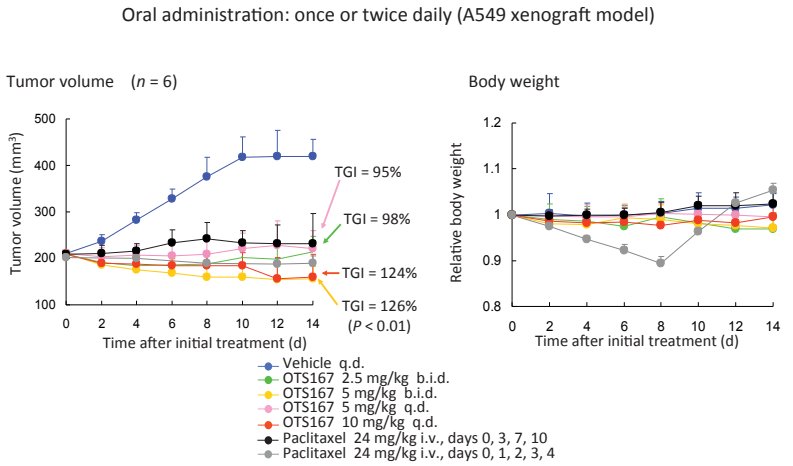

Figure 2: Therapeutic potential of oral OTS167 is more effective for tumor growth suppression than Paclitaxel with no severe side effects such as loss of body weight. Data taken from ref. 1.

OTS's esophageal cancer vaccine, S-588410, is now being tested in a phase III trial run by its partner Shionogi. S-588410 is also under evaluation in a phase II trial of people with bladder cancer. This trial, along with one on a head-and-neck cancer vaccine that Shionogi licensed from OTS, has now reached full enrollment and is in the follow-up stage. The other three vaccines developed by OTS—a colon-focused product partnered with Otsuka and a pair of liver cancer treatments out-licensed to Ono—are in phase I.

Supporting research through TCR-sequencing services

The third pillar of OTS's business is its T cell receptor (TCR)-sequencing service, an offering that makes the company's capabilities available to support the advance of personalized immunotherapy projects run by third-party research teams. OTS sees the service helping researchers in multiple ways, from improving their understanding of the interactions between cancer and the immune system to supporting the monitoring and assessment of ongoing oncology treatments. Data generated by the service can also guide patient selection and add to the understanding of drug mechanisms of action.

OTS delivers these insights using its TCR-sequencing platform, which involves a multistep process to derive genetic information that can be incorporated into clinic from blood and tumor samples. The process spans RNA extraction, cDNA synthesis, TCR sequencing and data analysis and provides OTS with clinical information that can inform cancer-drug development and suitable treatment choice. Although other companies also provide TCR-sequencing and data-analysis services, OTS's product is backed up by the experience and knowledge that the company has gained from its operations at the forefront of cancer research with Nakamura since the inception of the genomics era.

In the context of the TCR service, this experience translates into an offering with certain benefits in terms of the technical capabilities of the platform, the rigor of the process and the qualifications of the personnel performing the research. OTS goes beyond simply characterizing complementarity-determining region (CDR) 3 of TCR to deliver detailed insights into both TCR-α and TCR-β while also detecting unknown exons and taking steps to minimize polymerase chain reaction bias. The company can achieve all of this within six days. OTS extracts the maximum value from the data through its analysis algorithm.

Upcoming milestones

The upshot of OTS's long-running, multipronged drive to improve outcomes for cancer patients with unmet medical needs is that the company is now well placed to have an impact on the most closely watched area of drug development. A trio of its cancer peptide vaccines is in or approaching pivotal trials that could deliver the data that the company needs to win regulatory approvals, and OTS's unpartnered pipeline programs are also nearing inflection points. The next major milestones for the pipeline are upcoming data readouts from clinical proof-of-concept trials of two drugs, OTS167 and OTSA101, the latter of which is an antibody therapy for synovial sarcoma.

Once OTS has data from the clinical trials of OTS167 and OTSA101, it intends to step up its business-development activities. Out-licensing agreements for both programs could follow. Passing on the responsibility for further development to a partner would free OTS to focus its energy on its next-generation cancer therapies, which include drugs against six novel targets, and to continue the mission that it set for itself 15 years ago: to make a meaningful difference in the lives of patients by developing treatments that are both safer and more effective.

1. Chung *et al. Oncotarget* **3**(12), 1629–1640 (2012).

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