

Roche Partnering

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Roche outlines oncology partnering program

Roche's personalized healthcare strategy aims to provide medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients. The company is exploring external innovation and emerging technologies to help deliver on the application of this strategy for oncology.

Responding to the sustained high level of unmet medical need, Roche is investing 50% of its R&D budget in oncology and maintaining a strong focus on early R&D. This commitment to science-led innovation, alongside Roche's personalized healthcare strategy, is creating new opportunities for partnering at all stages of development in the Pharma Research and Early Development (pRED) program.

"We look for where we have the need and where we see the opportunity," said Hy Levitsky, head of Cancer Immunology Experimental Medicine at Roche's pRED program. "That ranges from research collaborations to target validation, through to assessment of compounds that are ready to go to the clinic or targets that are ready to be pursued all the way through to Phase 2 clinical trials."

Roche Partnering closely aligns its strategy with the pRED oncology program, identifying any gaps in the portfolio that could be filled by partners while remaining open to other opportunities. "We are always opportunistic, so if we can identify anything else that looks promising we will reach out to our research organization and check for a fit," said Stefan Frings, Head of Oncology-Immunology Partnering.

Science-led innovation

During the next few years, Roche expects new technologies to expand the current product portfolio for patients suffering from cancer, particularly in areas such as antibody-drug conjugates, synergistic therapy combinations and cancer immunotherapy.

"The last several years have marked a real shift in focus from purely cancer-intrinsic targets and pathways to those that examine the overall host-tumor interaction," explained Levitsky. "And that host-tumor interaction can be as it relates to angiogenesis, to the tumor microenvironment and supported stroma and, of course, to innate and adaptive immune responses to cancer."

Roche Partnering is actively seeking partners to bring in the first-in-class or best-in-class therapeutics for fields such as angiogenesis, antibody-drug conjugates and therapeutic antibodies. Roche's guiding principle is to seek partners that will complement the company's in-house expertise. "Roche has always had a nice balance between internal programs that emerge from our own discoveries, target assessment and compound validation, together with partnering or in-licensing of opportunities that perhaps give us a jump-start in areas that we are not yet that far along with," said Levitsky.

Cancer immunotherapy

Cancer immunotherapy is one area in which Roche has made a significant investment in recent years, including the appointment of Levitsky from the Johns Hopkins University School of Medicine in 2011. Alongside internal programs of work, such as new forms of antibody engineering, Roche has taken a strategic approach to partnering to get a head start in emerging areas like therapeutic cancer vaccines and modulators of myeloid cells within the tumor. Levitsky explained that partnering gave Roche access to compounds that were either already in the clinic or ready to go into the clinic, for use in early phase, proof-of-concept clinical trials. "We would then supplement those clinical experiments with our own 'newly minted' in-house approaches to those partnered targets," he added.

Roche is now at a pivotal point with cancer immunotherapy from a development perspective, according to Frings. "We better understand how cancer is evading immune system surveillance and how, from a therapeutic perspective, we can readjust the balance and get the immune system to recognize and attack the cancer again."

In this expanding field, Roche Partnering is looking for therapeutic modalities such as antibodies, small molecules and cancer vaccines to complement the existing pipeline that addresses the modulation of the tumor microenvironment. The ultimate aim is to engineer a systemic modulation of the host's immunity against cancers.

Target identification

Target identification is another area with good opportunities for partnering, according to Levitsky, as Roche's in-house expertise does not usually focus on target identification per se. "It's more about 'how do we target', 'how do we modulate', 'how can we engineer either a better antibody or a better small molecule'," he said.

"Very often the target has originated from the literature or from academic collaborators or in some cases from biotech that have invested in systems that reveal these targets," Levitsky noted. "This is another area where we spend a bit of time with our business development and partnering colleagues, to see if we can't find a good marriage between companies or groups that have found collections of attractive targets and our capacity to target them."

New platforms

The development of new platforms also offers potential opportunities for partnering. For

example, Roche is working in collaboration with the US National Cancer Institute to develop a platform for targeting cancer cells using a modified version of the potent cell killer pseudomonas exotoxin (PE). "We haven't disclosed the terms of the agreement with the NCI, but it is about access to a very interesting platform," said Frings.

The collaboration has resulted in a deimmunized version of PE that can be attached to antibody fragments or peptidic binders to create a cytolytic fusion protein (cFP). The hope is that the platform will enable the targeting of not only dividing cells but also slowly dividing and potentially even dormant cells. The aim is to have the first cFPs in Phase 2 trials by 2014. If data indicate clinical proof of concept, follow-on molecules targeting different targets and cancers could be developed quickly.

A new alpha-radioimmunotherapy platform for cancer is also being developed in collaboration with AREVA Med, a subsidiary of AREVA. The platform combines highly specific antibodies engineered by Roche with AREVA Med's radionuclide, Lead-212, to enable more precise irradiation of cancer cells while minimizing damage to healthy tissue. Under the terms of the agreement, Roche retains exclusive rights to commercialize the cancer radioimmunotherapy after clinical development.

Personalized health care

The oncology R&D program is also designed to deliver on Roche's personalized healthcare strategy, which covers better understanding of disease mechanisms, development of targeted treatments and identification of patients who will respond best to these targeted drugs. "Every project that we are pursuing has a very intentional and deliberate focus on personalized health care," said Levitsky. "The process of developing a candidate drug and a biomarker test to accompany that drug is now universally applied to virtually everything that we do."

The aim of developing companion diagnostics is to improve treatment outcomes by selecting suitable patients and monitoring the progress of therapy. Zelboraf (vemurafenib) is an obvious example because it is a targeted therapy that works only in patients who have the BRAF V600E mutation [See Box 1]. However, the concept is more broadly applicable. "Even in my own discipline of cancer immunology we are looking very hard at features of the tumor microenvironment and features of the patient's immune system that are likely to be predictive of a good response to immunotherapy," Levitsky said.



Roche's in-house expertise in both drug development (Roche Pharma) and diagnostic test development (Roche Diagnostics) means the company is well placed to deliver this integrated approach. So once the relationship between a biomarker and a drug has been established, a standardized companion diagnostic test can be developed and validated during clinical registration trials and, subsequently, prepared for regulatory approval alongside the drug.

Roche already has a broad portfolio of tumor markers, as well as a range of molecular oncology tests, but is always seeking opportunities for new assays and tests that can be developed for personalized health care. For example, Roche and Evotec entered a three-year agreement in 2011 to jointly develop new protein activity-based biomarkers for targeted cancer drugs. Evotec is using its PhosphoScout® platform to identify protein phosphorylations that predict favorable dosage and efficacy of targeted cancer drugs. Roche is conducting the clinical trials and assessing the development of companion diagnostics for patient stratification.

The integrated, personalized healthcare strategy also raises the bar for potential partners with promising drug candidates. Roche expects the majority of candidates to have at least an associated biomarker hypothesis.

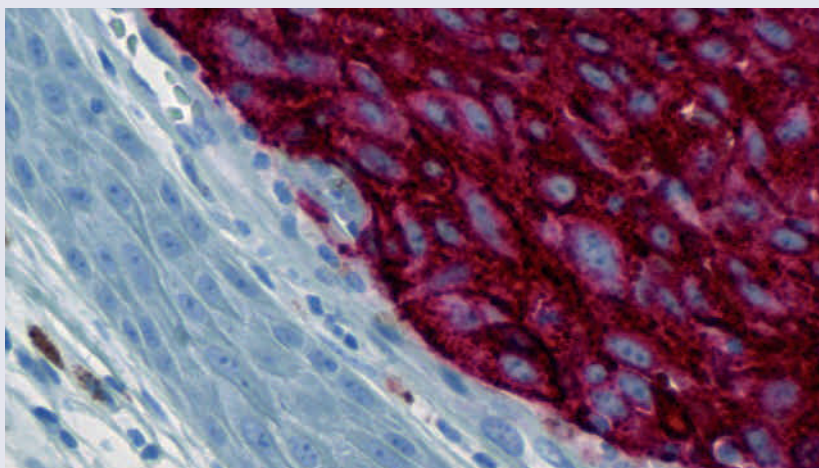
Benefits of partnering

The personalized approach carries through to Roche's partnering strategy, which focuses on creative deal structures tailored to each partner. "We always try to get a personalized deal," said Frings. "We consider a variety of deal types, ranging from licensing and acquisitions to option deals and portfolio agreements."

Alongside this flexible approach to dealmaking, partners also benefit from Roche's commitment to science-led innovation. "There's an incredibly rich set of resources available to partners who interact with Roche, from world-class, cutting-edge antibody engineering to a real commitment for things that are going into the clinic and a real commitment to study and nail down mechanisms of action in the very first early clinical trials," Levitsky explained.

"A great deal of investment goes into those biomarker studies and proof-of-principle studies where we hope for—but don't always expect—classical clinical responses from the candidates that go into the clinic. But we look for validation that the particular strategy is doing biologically what we are asking it to do, and that often suggests a better way to use it to maximize the probability of success."

The presence of Roche Diagnostics within the organization is a distinct advantage too, because it provides quick and easy access to expertise on any kind of diagnostic tool, from tissue diagnostics or PCR to other diagnostic and blood-screening tests.



Last year, vemurafenib was approved for the treatment of BRAF V600E mutation-associated malignant melanoma. Roche developed the therapy in partnership with Plexikon and concurrently developed a diagnostic to detect the mutation.

WIN-WIN PARTNERSHIPS

The recent success of the personalized cancer drug Zelboraf (vemurafenib), which selectively targets tumor cells with the BRAF V600E mutation, shows the benefits of a strong partnership when bringing a new treatment modality to market. Zelboraf (originally PLX4032) was co-developed under a 2006 license and collaboration agreement between Roche and Plexikon. The agreement included joint development of PLX4032 and other follow-on compounds targeting various BRAF kinase mutations.

Roche advanced the drug through Phase III clinical trials for malignant melanoma, which showed the compound to be considerably more effective than chemotherapy. Under a separate agreement, Roche Diagnostics co-developed a DNA-based diagnostic to identify patients whose tumors carry the

BRAF V600E mutation, which was done in parallel with the therapeutic development of Zelboraf.

"It was an attractive deal where both parties benefited," said Stefan Frings, head of oncology-immunology partnering at Roche. "A further advantage of partnering with a large pharmaceutical company like Roche is that we can come in and provide galenic expertise. So here, for example, the initial formulation was like brick dust, and in the Phase I trial we didn't achieve the required systemic levels with oral intake. It was only after pRED formulation scientists developed a microprecipitated formulation that meaningful plasma levels were achieved, which enabled vemurafenib to become the drug Zelboraf."

The collaboration succeeded in bringing the drug to market less than five years after the Investigational New Drug (IND) application.

Finally, partners benefit from Roche's proven track record in developing and commercializing oncology drugs. "If you work with Roche, you know that we have the inside knowledge to work successfully with the regulatory authorities, to develop—if required—the companion diagnostics dossier and the drug dossier in parallel, and to put in place the necessary testing in the field to identify patients that can benefit from the drug," Frings said. "Without this expertise, the launch of a novel treatment modality such as Zelboraf, which is driven by diagnostic tests, would not have been so successful."

Looking to the future, Levitsky believes the next set of major advances in cancer treatment will come from the intelligent use of combinations of agents, which will bring a new set of challenges

for pharmaceutical companies and partners alike.

"I think it is getting less and less likely that we are going to achieve major clinical impacts with the use of single agents," he said. "In fact, there are many strategies where we could even envision putting two agents together where one or even both of them do not have measurable single-agent activity. This is a big departure from classical cancer drug development, but it really is what the biology is dictating."

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