

Bridges and Barriers to Advancing CAR-T Therapy

Oncology therapy programs utilizing the latest immune mediated technology have exploded over the last decade. With the advance of checkpoint inhibitors, new and different molecular diagnostic tests, and more recently, engineered cell therapies, vast new avenues have opened up to effectively treat greater numbers of patients.

While these new therapeutic approaches have been welcomed scientific advances, their very specific design and development have limited the number of patients and tumor types that are appropriate for treatment. One development path that has been pursued is to study some therapeutics such as the chimeric antigen receptor T-Lymphocyte (CAR-T), that have been approved for hematological B-Cell Lymphomas, in both solid and hematological tumors. As the historical codex of Oncology has taught us, observing clinical effectiveness in one setting does not often translate to other settings whether it is different stages of the same disease or other tumor types that appear to share similar biological characteristics.

Kineticos' Operating Executive, Steve Buckanavage, recently caught up with Dr. Jeffrey Skolnik, VP of Clinical Development at Inovio Pharmaceuticals to discuss some of these very topics. Dr. Skolnik is currently responsible for overseeing global clinical development of assets for DNA immunotherapies for oncology at Inovio. Dr. Skolnik has over 10 years of experience leading early and late stage development programs in Oncology. He received his M.D. from New York University and pediatric training at Children's Hospital of Boston and completed his hematology / oncology training at the Children's Hospital of Philadelphia.

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Kineticos: Thanks for being with us today and sharing your perspective on our topic. Given your experience, and what you have seen in some development programs, what do you see as the evidence that supports co-development programs in both solid and hematological tumors?

JS: The strongest rationale to think about co-development programs in hematological malignancies and solid tumors would be the revolution we have seen over the last decade or

two really focusing on targeted therapies. Where we once were generic in our approach to treating particular cancers and sub-types of cancers with a nonspecific cytotoxic chemotherapeutic agents, we are no longer that specific with the way we approach our therapies. We know that different cytotoxic chemotherapies may affect different types of cancer cells differently, and there are going to be certain cancer types that will be more sensitive to chemotherapeutics or radiation therapy, for example.

In the past we have ironically focused our “nontargeted” chemotherapeutic/radiation therapies on specific, sensitive cancers. We tended to develop those individual agents in one specific disease, defined by a histological, rather than molecular, pathology. From a regulatory perspective, it had been easier to think about where we can approve drugs, not based on mechanism of action but based upon a disease subtype. However, most recently, we are seeing that it is mechanism of action-based therapeutics that are making a difference. Whether that is from targeted tyrosine kinase inhibitors, where we can look at a particular pathway that is disrupted across multiple tumor types, or most recently with the immuno-therapy revolution, where we can target different tumor types if they have the same pathway abnormality or if they would benefit from either adding to or disrupting basic immune mechanisms of the body. This allows us to look at several, very different, tumor types that we would not necessarily look at in the same clinical study, such as a hematological malignancy and a solid tumor, as long as the molecular pathology overlaps.

Kineticos: Historically, hematological malignancies and solid tumors have been viewed as completely different classifications and there was a higher standard to take a new approach or molecular entity into one or the other tumor type. This is an hourglass type of journey. We started at the wide end of this hour glass, a wide range and number of patients were available for treatment. As we start to understand the biological basis and defining characteristics of disease and pathways irrespective of the location of the tumor in the body, that has tended to narrow the patient population down. As it narrows down, you come into the narrow part of the hourglass with the expectation that there is higher efficacy or greater benefits to the patient. While we see some benefits to smaller groups of patients, does that feel like it is adding to or taking away from our ability to effectively treat patients?

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JS: It is interesting that you use “hourglass” as opposed to “funnel,” because a funnel is unidirectional; things moving through to the narrow end, never getting wider, whereas with an hourglass, the glass can be turned, allowing a broadening rather than just a narrowing. I wonder, as we continue to understand more on the molecular pathogenesis of cancer across multiple tumor types, if we will ever end up “flipping the hourglass” to broaden our disease sub-populations, instead of continuing to narrow them.

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By using sub-populations in which we are currently investigating new drugs, we believe the efficacy of new drugs will simply be better. We drill down into very specific molecular subtyping, mutational analyses, or mechanisms of action because it is assumed that the benefit is specific to that specific molecular sub-type, mutation, or gene signature. The justification for exposing a patient with the subsequent risks of that toxicity, or even better, avoiding the exposure of that therapy to someone who will not benefit from it, is helped by this sub-classification of different molecule sub-types. Even though we get into smaller and smaller sized populations, we can now successfully develop novel agents in those populations because the efficacy is better.

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The question of ‘In whom will this drug be the most helpful for the longest period of time,’ is what oncologists should ask when they see patients in the clinic. When you look at the standard checkpoint inhibitors, whether they are PD1, PD-L1, or CTLA-4 inhibitors, we know that, overall, only 20% of patients will receive clinical benefit in the form of an objective response. This means that for the majority of patients, we are doing nothing for them. We should not tolerate the chance of “no benefit” if you are getting a conventional chemotherapy or being forced to receive radiation every day for 6 weeks. Yet for the checkpoint inhibitors, we allow it because there is a real, durable, long-term benefit for many of those 20% of patients. We want to get to a place where we can identify the 20% of patients that will respond to a checkpoint inhibitor, or the 80% that will not and offer them something in addition,

something novel that will increase their chances of responding. If we cannot do that, then we must be able to identify the small population of patients that will benefit from the therapy, and limit the exposure of that drug to only that population. This is one way we can improve upon our ability to manage the benefit-risk balancing act for our patients.

Kineticos: Your example of the checkpoint inhibitors really illustrates the point of the question. When you have a group of patients who molecularly qualify for a checkpoint inhibitor, but only a few respond, that becomes the frustrating part. You are in the narrow part of the hourglass and the aspiration is how do we get to the other side of this bottleneck so that we can open up, find that ubiquitous key, pathway, or target receptor that enables us to prescribe with confidence so that the entire cohort will respond in a clinically meaningful way.

We talked about the benefits of being able to better target patients and go beyond the broad chemo/radiation/surgical approach. What about toxicology tradeoffs? Where do you think we are on this journey? While we see greater gains in efficacy for identifiable sub-populations, does that come with a commensurate risk?

JS: Yes, it can, specifically when your agent is targeting something that turns out to be important for vital life functions, organs, or tissue, but is coincidentally being expressed in your tumor, like HER2. We know HER2 is expressed in cardiac tissue, and we are looking at HER2-positive disease with a targeted treatment modality that also runs the risk of a specific, target-directed toxicity. If we look back at our core question, can you develop new molecules and therapies for both solid tumors and hematological malignancies simultaneously. We know it's possible with checkpoint inhibitors. You can treat Hodgkin's Lymphoma patients with PD-1 inhibitors, and see a remarkable response rate and, arguably, an improvement in progression-free and overall survival. You can also treat a solid tumor like non-small cell lung cancer with the same drug. The downside is that the toxicity seen with checkpoint inhibitors may be additive with the toxicities already seen secondary to, for example, a B cell malignancy like Hodgkin's disease. To date, toxicities in Hodgkin's disease to checkpoint inhibition have been similar to that seen in solid tumors, but over time we may see newer toxicities or dysregulation in the immune system specific to these patients.

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JS (cont): We always have to pay attention to what the novel agent or drug is doing. How does the cancer arise in the first place? Are those two things synergistic? Is there a reason to think the modality, the target itself, is going to be important in manifesting a toxicity? In the general cancer population, receiving a checkpoint inhibitor is thought to be easier than receiving a conventional cytotoxic. Toxicities like nausea, alopecia, mucositis are less likely, but the incidence of autoimmune disease like encephalitis, pneumonitis, kidney injury, and hepatitis are higher. Is there a specific patient population at risk for these events? Is there a specific tumor type at risk? We do not know yet.

Kineticos: I am reminded of the CAR T therapies, and while we see remarkable outcomes with B cell lymphomas. Certainly, some patients respond exceedingly well but what happens to otherwise healthy individuals with permanent “We always have to pay attention to what the novel agent or drug is doing. How does the cancer arise in the first place? Are those two things synergistic?” Bridges and Barriers to Advancing CAR T Therapy 4 B cell dysplasia?

JS: CAR T therapy is a fascinating new therapeutic modality that is changing and saving the lives of patients. When you are seeing patients, who have had evidence of residual disease after initial therapy, historically these patients do not live long. Patients have not been able to be “rescued” when progressing after first- or second-line therapy, for example in the adult leukemia population. To see 60% or 70% of patients who have been unresponsive to chemotherapy, and who respond with no evidence of disease following CAR T therapy, that is indeed miraculous.

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As we have gotten more comfortable and have started to see more programs for hematological malignancies with CAR T, there are studies out there researching CAR T therapy in solid malignancies. In general, these studies have been less positive clinically than the hematological malignancy CAR T therapy programs, and this gets to the mechanism of action.

It is easier to target cells that are floating through your blood stream or sitting in lymph nodes, waiting to head out to the periphery, with an antibody-based therapy or an engineered T cell-based therapy, whether it's a CAR T, a bi-specific T cell engager (BiTE), or an antibody drug conjugate (ADC), versus a solid bulk of tumor sitting in a compartment that is just not as accessible. It is also notable that CAR T cells are designed to attack specific cell-surface targets that, for example in leukemia, define their

mechanism of action and specifically hone in on the offending cancer cell. Whereas, you can target a CD19-positive B tumor cell for hematological malignancies, it has proven harder to do that for a solid tumor. While some cancer antigens are similarly co-expressed on normal tissue, as we discussed earlier with HER2, generally speaking, if you are expressing a cancer antigen, you can go after it.

It also turns out that you cannot obliterate whole organs the way you can the B cell compartment; we can return your B cell compartment to you, but it is harder to return normal epithelial tissue to you and is thus harder to do if you are looking at epithelial proteins that are expressed on a majority of normal tissue. Thus, co-development in the CAR T space in hematological malignancies and solid tumors at the same pace has been particularly challenging.

Kineticos: While there has been great progress in translating newfound understanding of the basis of disease into clinically meaningful medicines, it seems we have entered the narrow part of the hour glass. Certainly, there are reasons to celebrate in terms of achieving better outcomes. Yet, much more work remains as we focus on developing ways for broader patient populations to benefit from these discoveries.

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