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Immuno-Oncology: Scratching The Surface

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Another day, another announcement about great data from immuno-oncology. It's clearly one of the hottest fields in biopharma today, and has been for a few years. The opening paragraph of a recent Leerink report by Seamus Fernandez and team on I/O is a great summary of the field today:

> *Others may complain about 'IO fatigue' but we can't get enough of it. Biopharma companies are changing the way we treat cancer by unleashing the immune system, achieving functional cures in several of the most deadly cancers. The breadth, durability, and tolerability of PD1/PDL1 antibodies demonstrated over the last three years should establish this class as the backbone of a new pillar of cancer care, immuno-oncology.*

And it goes beyond the PD-1 axis; as Leerink notes, and was highlighted in this 2013 NEJM paper, the race for the best combinations with synergistic efficacy is well underway. The current wave of late stage therapeutics represent a $40B-plus market opportunity (again according to Leerink), with significant portfolios at Novartis, BMS, Merck, Amgen, AZ, and others. We and other venture firms have been quite active in the space. Earlier this year, Novartis acquired CoStim Pharmaceuticals, an immuno-oncology checkpoint inhibitor company backed by MPM and Atlas (here); we've also been supporting bispecific antibody programs in the checkpoint and I/O space at F-star (here).

Stepping back from the business aspects, the big advantage of immuno-oncology is its adaptive anti-cancer mechanism. As an individual's cancer evolves and mutates, the patient's immune system evolves its anti-tumor response – made possible by either removing the brakes or stepping on the gas via these new I/O therapies.

This isn't a new concept, or a new field. During my training in immunology two decades ago, immuno-oncology concepts were also hot. Lots of enthusiasm (and funding) underpinned the first wave of cancer vaccines: tumor lysates, defined epitope cassettes, DNA vaccination, etc... And although it was relatively easy to induce proliferation of tumor-antigen directed T-cells, they largely weren't effective *in vivo*. Over the intervening period, researchers elucidated that tumors evaded these tumor-directed T-cells by subverting immune checkpoint pathways and other immune-regulatory mechanisms. This insight, among others, is what unlocked the potential for I/O therapies to enable a functional immune response that is tailored in a patient to their particular tumor.

I/O represents the ultimate in personalized medicine, as the tumor antigens and specific epitopes leading to T-cell mediated tumor destruction in any given patient are likely different. The mechanisms and targets of tumor killing are likely both polyclonal (T-cells emerge against a number of different tumor-specific epitopes) and dynamic (they change over time); this is in direct contrast to the static and singular mechanism of action of most other therapeutics (inhibiting a tyrosine kinase, for instance). As my colleague Michael Gladstone likes to say "immuno-oncology is about shooting a moving target with a moving arrow."

Given the impressive survival data over the past five years, the field of I/O is becoming incredibly crowded and competitive, especially for the first generation of targets (e.g., CTLA-4, PD-1/PD-L1, TIM3, LAG3, OX40, etc). Partnering deals seem to be happening every day, with new entrants touting different therapeutics against these targets. It will be interesting to see how the landscape evolves, especially as payors weigh in (in light of HCV payor deals recently).

These first generation targets are largely aimed at taking the brakes off of the immune system (avoiding/reversing T cell suppression by the tumor). While the responses are very impressive, efficacy has been largely limited to a "subset of patients with a subset of cancers". To date, we've only witnessed modest benefits in other major tumor types (the big four), and durability of efficacy in the immuno-responsive tumors (melanoma, lung, RCC, etc) in the majority of patients remains a question.

We're big believers that we are no where near "peak I/O" as a clinical research community - we are the front edge of a wave of new therapies and immune-directed targets, and their combinations, that offer real promise to broaden, deepen, and extend the longevity of immunotherapy benefit.

A big part of this wave will be therapeutics that target other immune components beyond effector T cells: T-regulatory cells, antigen-presenting cells, myeloid suppressor cells like tumor-associated macrophages, etc... These non-T-cell directed approaches have emerging validation in cancer therapy: CSF1R inhibition for TAM repolarization (Roche, here), IDO inhibitors directed to a suppressive mechanism of T-regs (Incyte, Newlink, and their many partners), and CD40 agonists to improve APC function (here).

By targeting additional axes of the immune system (especially other cell types), we expect to be able to address other tumor types (e.g., where T cells are not anti-PD-1 responsive due to other repression mechanisms) and synergize with T cell-directed therapies.

Unveiling Surface.

These orthogonal I/O approaches are where Atlas' new startup, Surface Oncology, has been focusing, with multiple programs underway targeting novel mechanisms and biology to modulate several major "components" described above beyond T-cells.

Emerging (and largely unpublished) preclinical validation, from cancer patient tumors and their cellular infiltrates, as well as animal models, has

identified each of these programs as having potential to expand and broaden immunotherapy's efficacy, both in monotherapy and in combo with effector T cell-directed agents, e.g.: several emerging cytokines/metabolites that accumulate in the tumor microenvironment to broadly suppressive multiple immune cells; novel pathways involved in myeloid cell function and repolarization from an immunosuppressive phenotype to an immuno-stimulatory phenotype; and, new targets critical for tumor-specific T-reg function, among others.

Initially seeded in early 2014 and incubated at Atlas Venture, the company recently closed a $35 million Series A financing round (press release here), led by Atlas, Fidelity, Lilly Ventures, and NEA, with participation from our two Corporate Strategic Partners, Novartis Institute for Biomedical Research (NIBR) and Amgen Ventures, and a personal investment from Elliott Sigal, the former head of R&D at BMS. We're very pleased with the great mix of investors that helped drive and fine-tune Surface's plan alongside us.

Surface is led by acting CEO Dave Grayzel, a partner at Atlas; former CEO of Arteaus Therapeutics and Annovation, both Atlas-backed companies. Dave, Michael Gladstone, and Venture Partner Josh Resnick quarterbacked Surface's ideation and foundation, bolstered by experienced entrepreneurs from the Atlas network, including the company's Chief Technical Officer, Scott Chappel (founder and CSO of Arteaus), and our VP of Corp Dev and IP, Nick Buffinger (who played a critical role in the construction and execution at CoStim).

The company's scientific founders and SAB are comprised of world-leading immunologists and cancer researchers, whose work will shape the future development and expansion of the cancer immunotherapy landscape, including co-chairs Sasha Rudensky (Memorial Sloan Kettering) and Arlene Sharpe (Harvard/DFCI). They are joined on the SAB by Christopher Hunter (Penn), Carla Rothlin (Yale), Elliott Sigal, John Stagg (Montreal), and John Wherry (Penn). It's an impressive

founder and advisory group, with a great emerging team behind the Surface story.

We're expecting great things from Surface, and continued excitement about the impact of new immune-directed approaches on cancer patient care.

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