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A tribute to the life and career of Holbrook Kohrt

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Holbrook Kohrt, a key inspiring and influential leader in the new field of immuno-oncology, passed away at the height of his professional life on February 24th 2016, aged 38. This devastating news has left many in the immuno-oncology community with a huge sense of loss and sadness.

Until the very end, Holbrook has been entirely dedicated to simultaneously fight against two diseases. The first was hemophilia, which he fought as a patient, and which eventually took him over. The second was cancer, which he fought as a doctor and researcher in hematology and immunology to which he made major contributions.

People who got a chance to know Holbrook quickly realized that he was clearly in a league of his own. Looking at his curriculum shows how amazing he was to have accomplished so many things in such a short amount of time. Holbrook successfully graduated from Stanford University with both an MD and PhD. There he carried out two post-doctoral fellowships in parallel in the renowned laboratories of Prof. Sam Strober & Prof. Ron Levy. Thanks to his talent, productivity and hard work, Holbrook became an assistant professor at Stanford and led an active research group until his last days. Holbrook authored more than a hundred scientific papers, gave hundreds of educational talks and seminars, and took care of many patients with complete dedication. He was the principal investigator of several cancer immunotherapy clinical trials and research projects and worked relentlessly as an expert and advisor for many in both academia and industry. Holbrook was a member of multiple scientific advisory boards in the biotech industry and the co-founder of ovacure.org, a non-profit organization for ovarian cancer. With a full MD, PhD training and a daily practice of scientific and clinical research, Holbrook was one of those rare individuals with a true medical and scientific profile. His expertise in immuno-oncology made him even more valuable in the current era of cancer immunotherapy.

The initial focus of his work was on allogeneic stem cell transplantation and cancer vaccines (see his last review on the topic in Annals of Oncology; Tan A et al. Ten Challenges to

Success: Past and Present of Ten Cancer Vaccines, in press). However, Holbrook quickly identified the therapeutic potential of immune checkpoint targeted antibodies for treating cancers. He chose to focus on one of them, CD137 (also called 4-1BB) [1]. One of his major achievements was to demonstrate how immunomodulatory antibodies can boost NK-cell mediated anti-tumor immunity. He first observed that upon passive immunotherapy with anti-tumor monoclonal antibodies (mAbs), mouse and human NK cells up-regulate CD137 on their surface upon activation of Fc-gamma receptors through antibody derived cell cytotoxicity (ADCC). He then nicely demonstrated that combining anti-tumor mAbs with agonistic anti-CD137 mAbs could boost NK cell-induced ADCC and synergize *in vivo* in tumor-bearing mice. He did a tremendous amount of work to demonstrate that the upregulation of CD137 on NK cells and ADCC enhancement by anti-CD137 mAbs was a common phenomenon seen both in mouse and human B-cell lymphoma treated with anti-CD20 mAbs [2], in HER-2+ breast cancer treated with anti-HER2 mAbs [3] and in head and neck squamous cell carcinomas (HNSCC) treated with anti-EGFR mAbs [4]. These results brought early and important insights regarding i) new rational combinations with immunomodulatory mAbs, particularly with tumor-directed mAbs, and ii) the capacity of immunomodulatory mAbs to stimulate innate immunity (in addition to adaptive immunity) against cancer. This pre-clinical work gave rise to several clinical trials (NCT01307267 and NCT01775631).

Interestingly, Holbrook demonstrated three major critical aspects of such tumor-targeted and immune-targeted combinations. First, that it takes several hours to upregulate CD137 on NK cells and that timing is critical when combining tumor-targeted mAbs and anti-CD137 mAbs: co-injections of the two antibodies at the same time would have no synergy whereas waiting 24h after the tumor targeted mAb and before injecting the anti-CD137 would provide full synergy. Second, that passive immunotherapy with anti-EGFR antibody therapy (cetuximab) actually elicits an adaptive anti-EGFR CD8+ T-cell immune response in patients with HNSCC. Third, that the combination of anti-EGFR and anti-CD137 antibodies generates a polyclonal anti-tumor CD8+ T-cell immune response *in vivo* against both $EGFR^{pos}$ and $EGFR^{neg}$ tumors. These observations support the fact that anti-CD137 Abs can enhance the

“vaccinal effect” and favor “epitope spreading” of anti-tumor mAbs [5]. The preliminary results of the ongoing clinical trial combining rituximab and anti-CD137 suggest that such synergistic combinations might well translate into the clinic for patients with rituximab refractory B-cell lymphomas [6]. Pursuing on innate immune cells immunomodulation and NK cells immune checkpoint targeted mAbs, Holbrook also demonstrated that anti-KIR antibodies synergize efficiently with anti-CD20 antibodies in pre-clinical models of B-cell lymphomas, providing a pre-clinical rationale for a future lirilumab and rituximab combination trial [7].

Besides his major focus on NK cells, Holbrook has been instrumental in moving forward multiple collaborative projects in which he believed the scientific question needed to be addressed. For instance, Holbrook contributed to the development of the *in situ* immunization strategy and translated the intra-tumoral anti-CTLA-4 approach very quickly to the clinic (NCT01769222 and [8]). He was also involved in demonstrating the synergistic combination of ibrutinib, a BTK inhibitor, with immunotherapy [9,10]. His impressive network of collaborators allowed him to contribute to major cancer immunotherapy and tumor immunology projects [11–17].

We had the immense privilege of becoming colleagues, collaborators and close friends of Holbrook while spending thousands of hours working with him during our post-docs at Stanford. His bright mind, incredible focus and amazing work capacity amazed all of us. His generosity and care for people around him was limitless. Holbrook did not like politics in science, ego-driven investigators, and endless meetings. All these common issues were a waste of time, and he understood early on with his life-threatening disease that time is a scarce resource. Holbrook loved to have discussions on the science around cancer immunology, but these discussions would always finish with a clear definition of what we should do next and what would be the next experiment plan. He was very enthusiastic about opportunities for new projects and collaborations. Such collaborations have been an important part of his career and, indeed, Holbrook was keen to share his knowledge and expertise with everyone and was prone to sharing samples and experimental data for the

advancement of a scientific or clinical project. He was modest about his own achievements and was quick to recognize the achievements of others. In 2015, Holbrook became a member of the editorial board of Annals of Oncology. He was a meticulous referee and editor and his work for Annals was much appreciated by the journal staff and authors alike.

In all of his work, Holbrook brought three enduring characteristics: dedication, focus, and strategy. He also exercised crystal clear pedagogy, distilling the most complex immune phenomenon into a series of simple steps. This skill was highly appreciated by his students and colleagues, whether this was for a basic science course or advice for the strategic development of a biotech company. Finally, he always kept a clear sense of purpose, making sure neither he nor his colleagues ever lost sight of the larger goals of advancing medical knowledge and saving lives. Through both his words and actions, he taught us not just about medicine and science, but about life, friendship, dedication, and focus. Beyond his scientific legacy, Holbrook is survived by his family and his numerous friends and colleagues. We extend our deepest condolences to them. Holbrook will be deeply missed by us all.

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Picture of Holbrook

Holbrook Edwin Alan KOHRT (1977-2016)

