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Rational design of immune checkpoints' small molecule inhibitors

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T lymphocytes preserve the immunological balance between defending against viral infection and preventing continual activated immune responses. While T cells' specificity against cancer or viral infection is determined by the interaction between the T-cell receptor complex (TCR) and antigenic peptides bound in surface major histocompatibility complex (MHC) molecules, the full activation of T cells requires a second signal obtained by the binding of the co-receptor CD28 on T cells to CD80/86 molecules on activated antigen presenting cells (APCs). Once mobilized, T cells also express other receptors that inhibit their proliferation and cytokine production, known as immune checkpoints. Among these receptors are Cytotoxic T Lymphocyte Antigen-4 (CTLA-4), programmed death-1 (PD-1) and T cell immunoglobulin mucin-3 (TIM-3) and many others. Blocking the interactions between these receptors and their ligands emerged as a 'game changer' in immunotherapy, with antibodies directed toward PD-1, for example, being selected as 'drug of the year' for 2013 by Science. More importantly, combination blockage of multiple co-inhibitory pathways has a greater efficacy by preventing accumulation of the unblocked negative co-receptor, allowing T cells to continue to survive, proliferate, and carry out effector functions within infected cells. This talk will focus on PD-1 and will describe for the first time two accurate models for human PD-1 bound to its two human ligands. The talk will also demonstrate how these two models are being used to rationally design small molecule inhibitors for the Pd-1 pathway.

Biography

Khaled Barakat is an Assistant Professor at the School of Pharmacy at the University of Alberta, Canada. His research stands at the multidisciplinary interface of physics, biology and computer science. His major focus is on developing and applying state-of-the-art computational drug discovery tools to discover new antiviral and immunotherapeutic drugs. He has made great contributions in understanding the nature and biophysical processes underlying protein–drug, protein–protein and drug off-target interactions and predicting drug-mediated toxicity. He also received numerous awards including the CIHR and AIHS postdoctoral fellowships, the prestigious University of Alberta dissertation award and many distinction awards throughout his undergraduate and graduate studies. He is also the Editor of the *Journal of Pharmaceutical Care & Health Systems* and serves as a guest reviewer for several journals.

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