Engineering cytokine immunotherapies via cell surface targeting
by
Luciano Santollani
April 30th 2:30 pm
Luria Auditorium

Cancer immunotherapy targets immune cells to trigger a highly specific, long-lasting anti-tumor response. With the clinical success of immune checkpoint blockade and the development of promising next-generation agents, immunotherapy is steadily growing as a key pillar of the oncology clinic alongside surgery, radiation, and chemotherapy. Cytokines, endogenous regulators of immune responses, have long been promising immunotherapy candidates due to their innate ability to modulate lymphocyte behavior. However, translation of cytokines as systemically administered immunotherapies has been severely limited by off-target/toxicity. One approach to overcome this challenge is to engineer cytokines for intratumoral retention following local administration to isolate their activity to on-target tissue. In this thesis, we explore an immune cell-based localization strategy by designing, evaluating, and optimizing antibody-cytokine fusions targeting the ubiquitous leukocyte receptor CD45.

First, we engineer and profile an αCD45-IL15 fusion that exhibits significantly diminished receptor-mediated internalization relative to its wild-type counterpart. This extended surface half-life augments downstream pSTAT5 induction and enables both cis and trans signaling between lymphocytes. We demonstrate this enhanced cell-surface biology is consistent when this approach is applied to another pro-inflammatory cytokine, IL-12. Preliminary experiments additionally suggest conserved behavior between mouse and human CD45-targeted cytokines. Intratumoral αCD45-cytokine administration at specified doses leads to decoration of leukocytes in the tumor and tumor-draining lymph node (TDLN) while sparing systemic exposure. CD45-targeted proteins drain in a dose-dependent manner from the tumor through the TDLN and into systemic circulation, allowing for compartment specific targeting.

In the second part of the thesis, we develop and deeply characterize a two-dose sequential cytokine therapy termed αCD45-Cyt that safely elicits profound anti-tumor immunity. In this paradigm, a single dose of αCD45-IL12 followed by a single dose of αCD45-IL15 is able to eradicate both treated tumors and untreated distal lesions in multiple syngeneic mouse tumor models. Mechanistically, the improved intratumoral and nodal retention driven by CD45 targeting enabled reprogramming of tumor specific CD8+ T cells in the TDLN to exhibit an anti-viral transcriptional signature. Finally, we discuss preliminary data and plans for translating αCD45-Cyt therapy. Altogether, this thesis highlights the power of targeting host immune cells for use in immunotherapy and more broadly discusses the ability of multi-receptor targeting to elicit new cytokine signaling biology.

Thesis supervisors: K. Dane Wittrup, PhD; Darrell J. Irvine, PhD
Title: Carbon P. Dubbs Professor of Chemical Engineering and Biological Engineering (KDW); Underwood-Prescott Professor of Biological Engineering (DJI)
Thesis Committee Members

K. Dane Wittrup, PhD (Thesis Advisor)
Carbon P. Dubbs Professor of Chemical Engineering
Professor of Biological Engineering
Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology

Darrell J. Irvine, PhD (Thesis Advisor)
Underwood-Prescott Professor of Biological Engineering
Professor of Material Science
Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology

Paula T. Hammond, PhD (Thesis Presider)
Institute Professor
Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology

Ulrich von Andrian, MD, PhD
Mallinckrodt Professor of Immunopathology at Harvard Medical School
Program Leader, Basic Immunology at Ragon Institute of MGH, MIT and Harvard