Informatics tools for identification, prioritization and clinical application of neoantigens (pVACTools)

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The goal of one class of cancer immunotherapy is to leverage the immune system’s ability to attack non-self or “foreign” cells (recognized by their neoantigens). Personalized neoantigen vaccines and checkpoint inhibition therapies (e.g. Pembrolizumab) are two examples of this type of cancer immunotherapy.
Advances in sequencing technology allow for rapid identification of neoantigen candidates.
Invoking an adaptive immune response against the tumor

1. **Tumor** produces a unique peptide corresponding to a somatic mutation

2. **Processing** and presentation of the tumor specific peptide

3. **Neoantigen** peptide presented by MHC

4. T cell receptor that uniquely matches the tumor peptide
Neoantigen prediction is a major biology and informatics challenge

Almost infinite diversity of TCR sequences/structures

2.2 x 10^{14} possible 8-11mer peptides (2.2 hundred trillion)

>5,000 known HLA alleles (not counting somatic alterations of MHC)

**Many** other supporting factors both upstream and downstream of this complex needed for a therapeutic response

http://pdb101.rcsb.org/motm/63
Identifying and characterizing neoantigens is critical for understanding response to checkpoint inhibitors and designing personalized cancer vaccines and other emerging immunotherapies.
Neoantigen characterization relies on a very complex workflow
pVACtools (pvactools.org) was created to facilitate neoantigen identification/prioritization for a variety of downstream applications.
pVACtools is an open source modular tool kit

- Goal is to create a tool suite that supports a broad user group with neoantigen analysis needs
  - Multiple organisms
  - Basic science -> clinical trials
  - Multiple therapeutic modalities

- Implemented in Python3
- Leverages IEDB API, VaxRank, MHCflurry, MHCNuggets, and other open source efforts
- [https://github.com/griffithlab/pVACtools](https://github.com/griffithlab/pVACtools)
- License
  - Was NPOS 3.0, next release will be BSD
- Documentation
  - [http://pvactools.org/](http://pvactools.org/)
  - [http://pmbio.org/](http://pmbio.org/)
- CWL/Cromwell/Docker pipelines
  - [https://github.com/genome/analysis-workflows](https://github.com/genome/analysis-workflows)
pVACtools development will be guided in part by the needs of ongoing personalized cancer vaccine trials at WASHU and elsewhere.

Personalized cancer vaccine trials providing input:

- Kidney Cancer (n = 15 patients)
  - NCT03598816 (James Hsieh)
- Glioblastoma (n = 30 patients)
  - NCT03422094 (Gavin Dunn)
- Breast Cancer (n = 54 patients)
  - NCT02348320 (William Gillanders)
  - NCT03199040 (William Gillanders)
- Follicular Lymphoma (n = 20 patients)
  - NCT03121677 (Todd Fehniger)
- Prostate Cancer (n = 20 patients)
  - NCT03532217 (Russell Pachynski)
- Pancreatic Cancer (n = 15 patients)
  - NCT03122106 (William Gillanders / Daniel Laheru)
- Melanoma (n = 12 patients)
  - NCT03092453 (Beatriz Carreno / Gerald Linnette)
- Colorectal Cancer (n = 12 patients)
  - NCT03730948 (Beatriz Carreno / Kim Reiss-Binder)
Specific aims

• **Aim 1.** Develop a software toolkit for comprehensive identification and characterization of neoantigens

• **Aim 2.** Enhance prioritization of neoantigens by elucidating key factors that influence immunogenicity

• **Aim 3.** Assess predictive value of neoantigen tools using clinical trial data
Relevant publications


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