

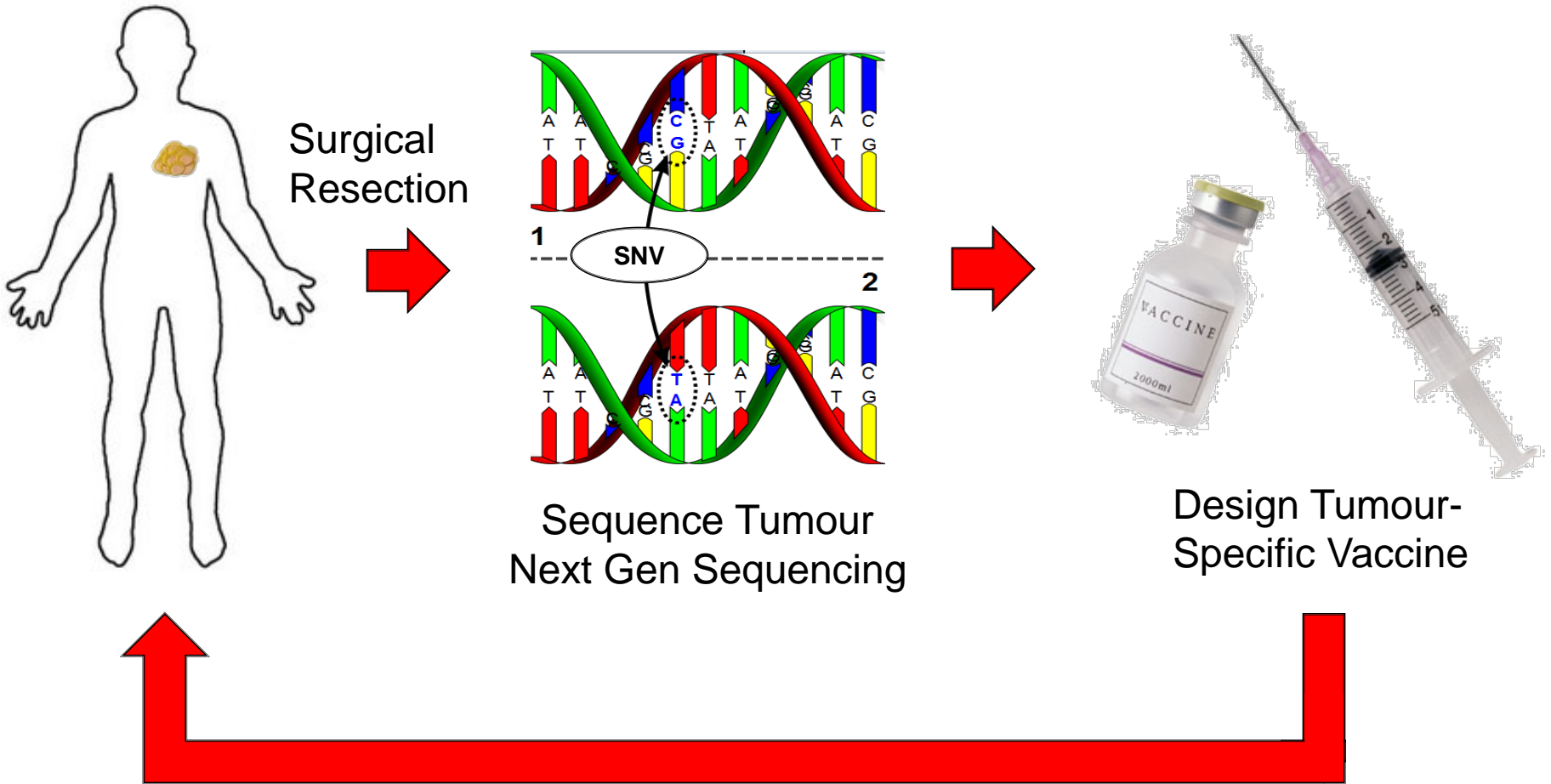
Personalized Vaccines Targeting Tumour-Specific Mutations

Spencer Martin (PhD Candidate)

Dr. Brad Nelson (DRC)

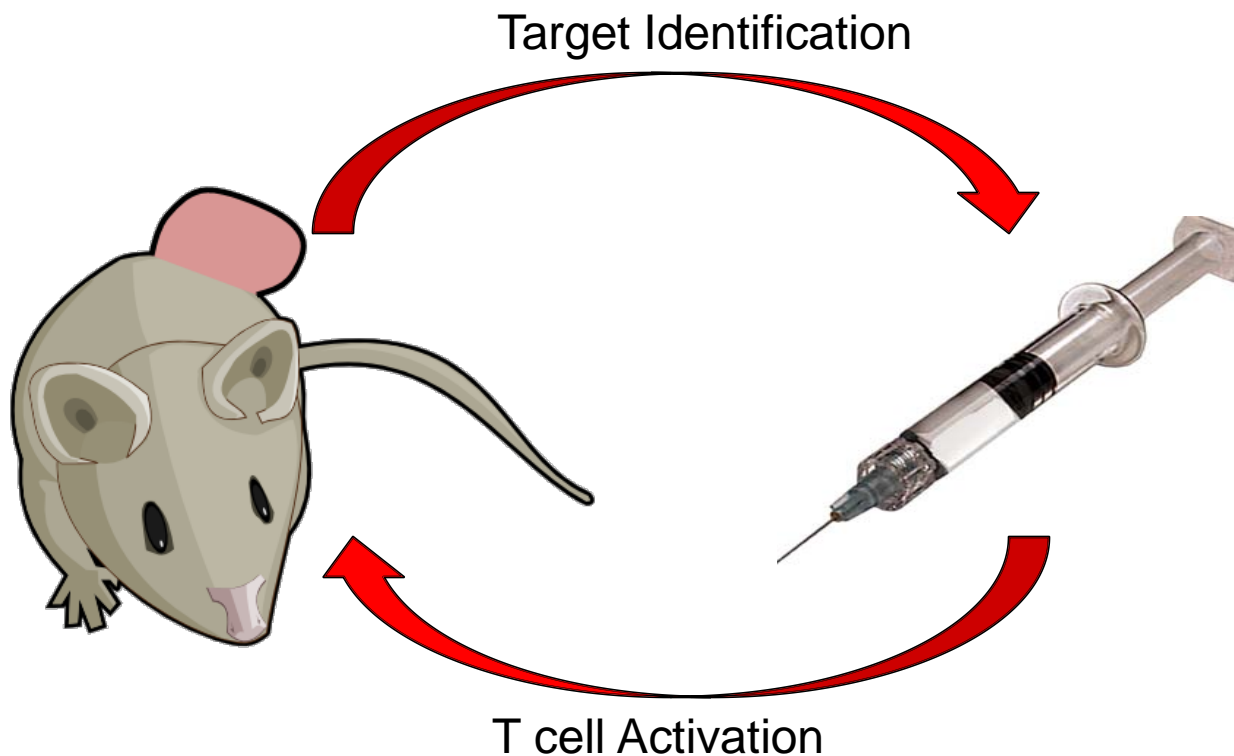
Dr. Robert Holt (GSC)

The Goal: Personalized Vaccines



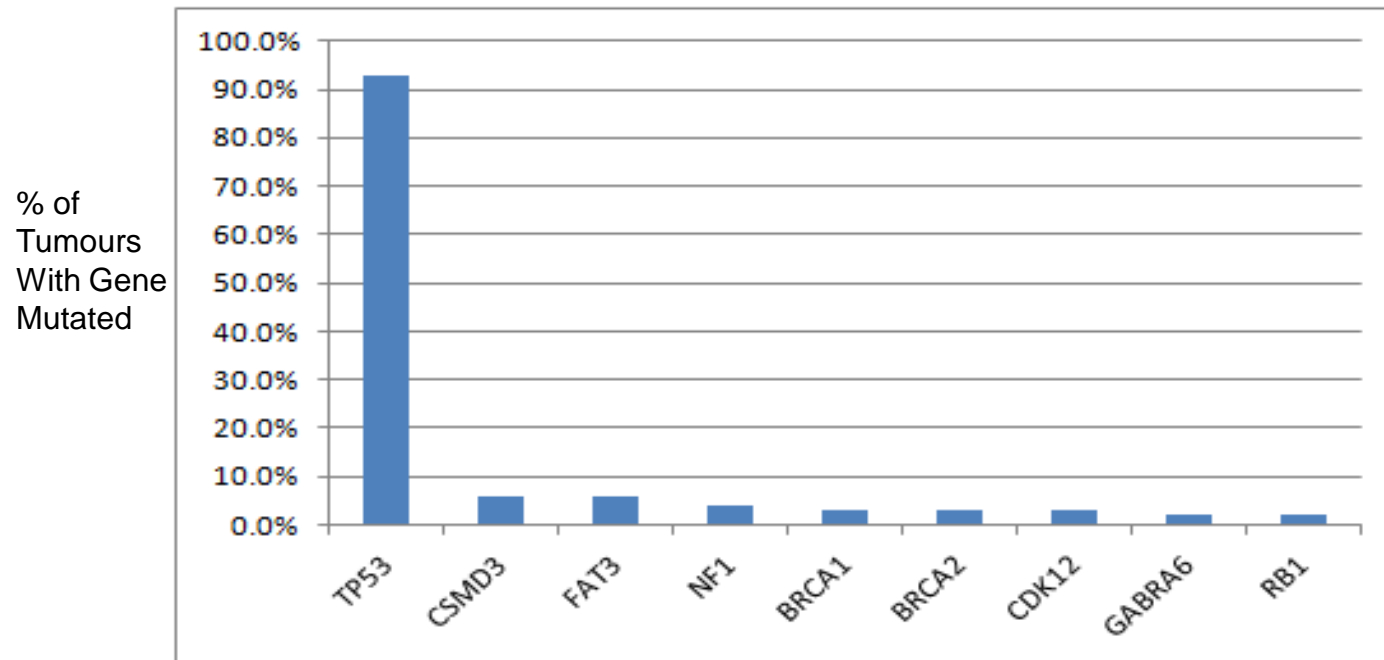
Project Objectives

1. To identify tumour specific somatic mutations
2. To activate T cells towards tumour specific mutations



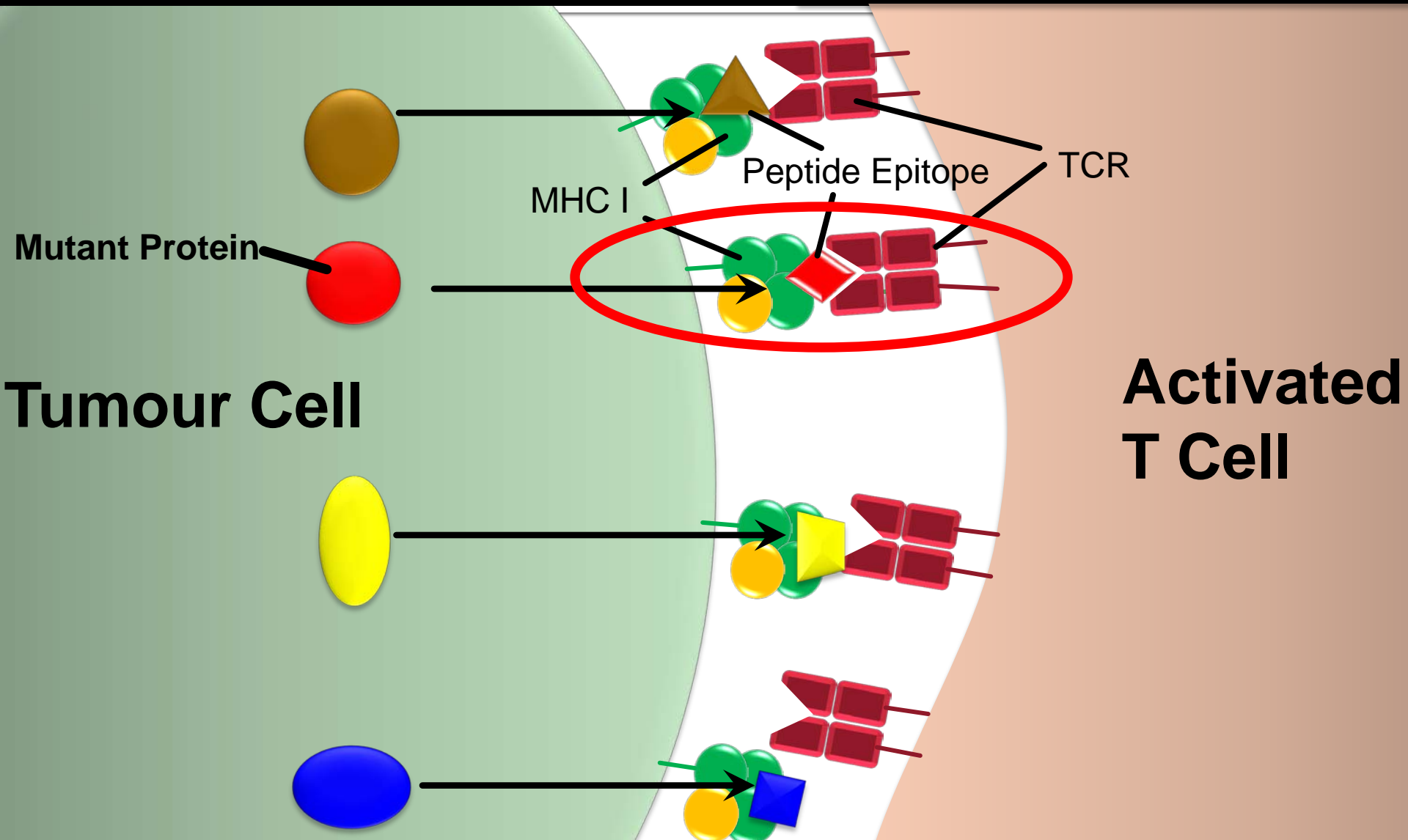
Next Gen Seq and Cancer: Every Tumour has a Unique Mutational Profile

TCGA Ovarian Cancer Project

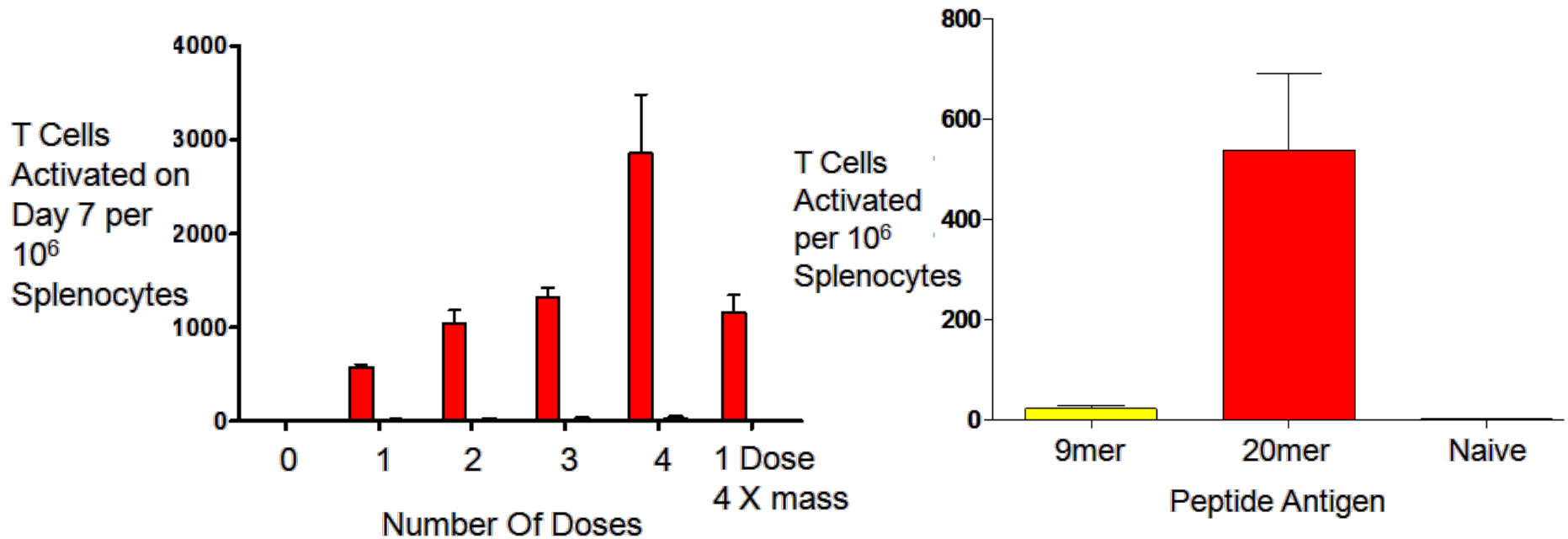


- 13,000 coding mutations in 316 ovarian tumours
- The only gene that was mutated in > 10% of all tumours was p53.

The Immune System Recognizes and Destroys Cells With Mutant Proteins



Cluster Vaccination Effectively Activates T Cells



- Vaccinated mice with protein antigen plus adjuvant poly(I:C)
- Measured T cell activation on day 7
- Vaccinating on 4 consecutive days (cluster vaccination) was more effective than any fewer days

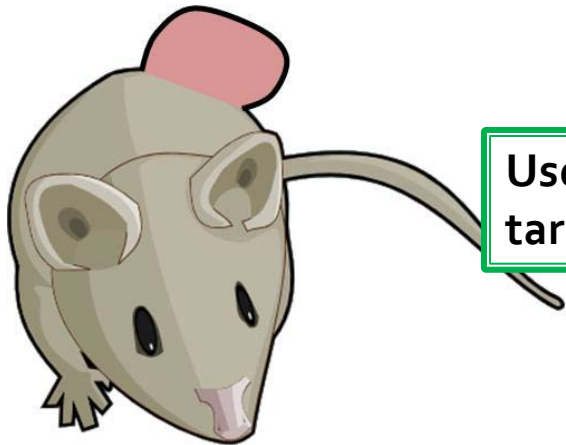
Profound CD8⁺ T cell immunity elicited by sequential daily immunization with exogenous antigen plus the TLR3 agonist poly(I:C)

Darin A. Wick^a, Spencer D. Martin^{a,b}, Brad H. Nelson^{a,b}, John R. Webb^{a,b,*}

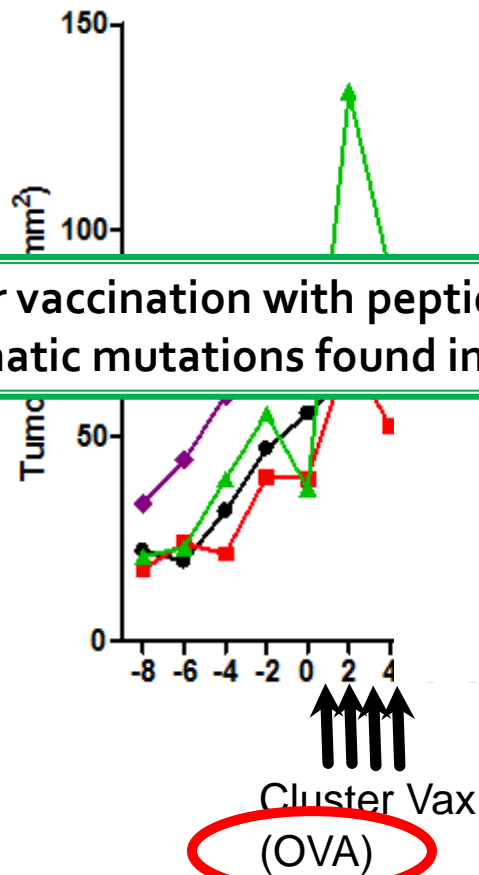
Cluster Vaccination Eliminates NOP23 Tumours

NOP23 Mouse Model Of Breast Cancer

- TG - Dominant Negative p53
- TG - Mutant Her2/neu + OVA tag

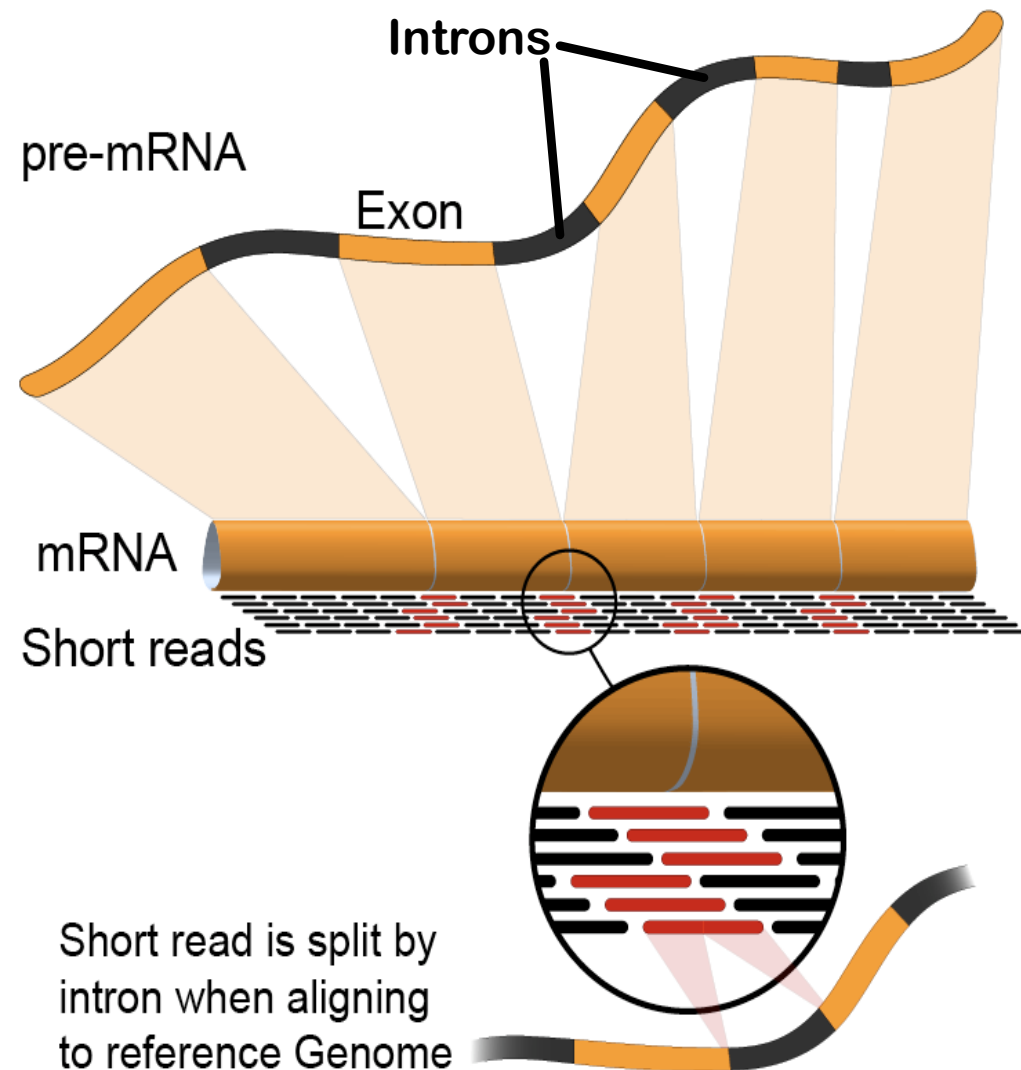


Use cluster vaccination with peptide antigens that target somatic mutations found in the tumour



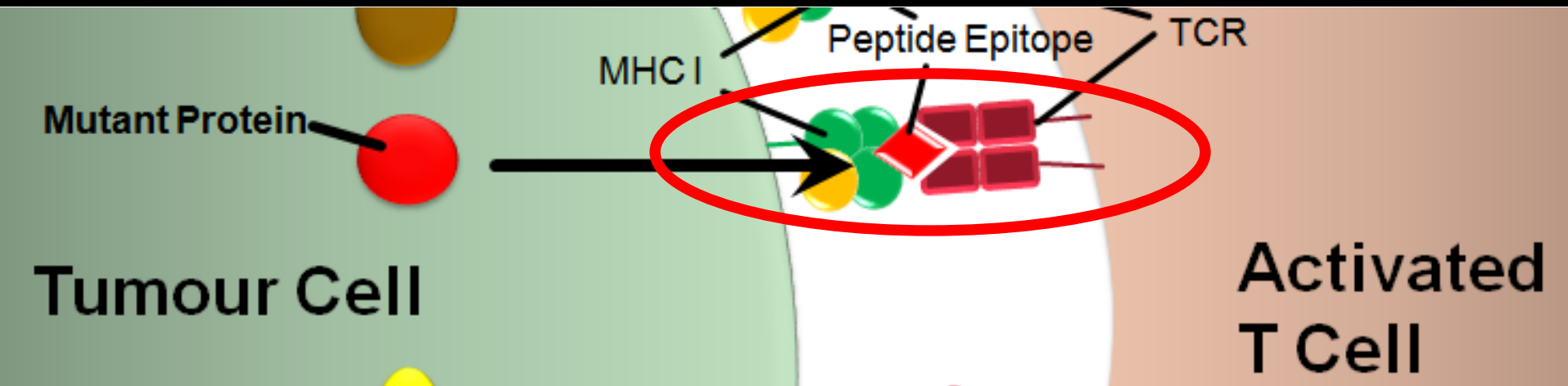
Courtesy Dr. Sally Amos

RNA-Seq Identified 4 SNVs and 2 Fusions in NOP23



Tumour Line	NOP23
Total Reads	202,704,168
Chastity Passed	192,194,212
Reads Aligned	110,251,246
Bases Aligned	11,025,124,600

1st Mutation Target: Llg12



- R705H is predicted to be in an MHC I binding epitope (IEDB)
- R705H is predicted to be deleterious to the Llg12 protein (SIFT)

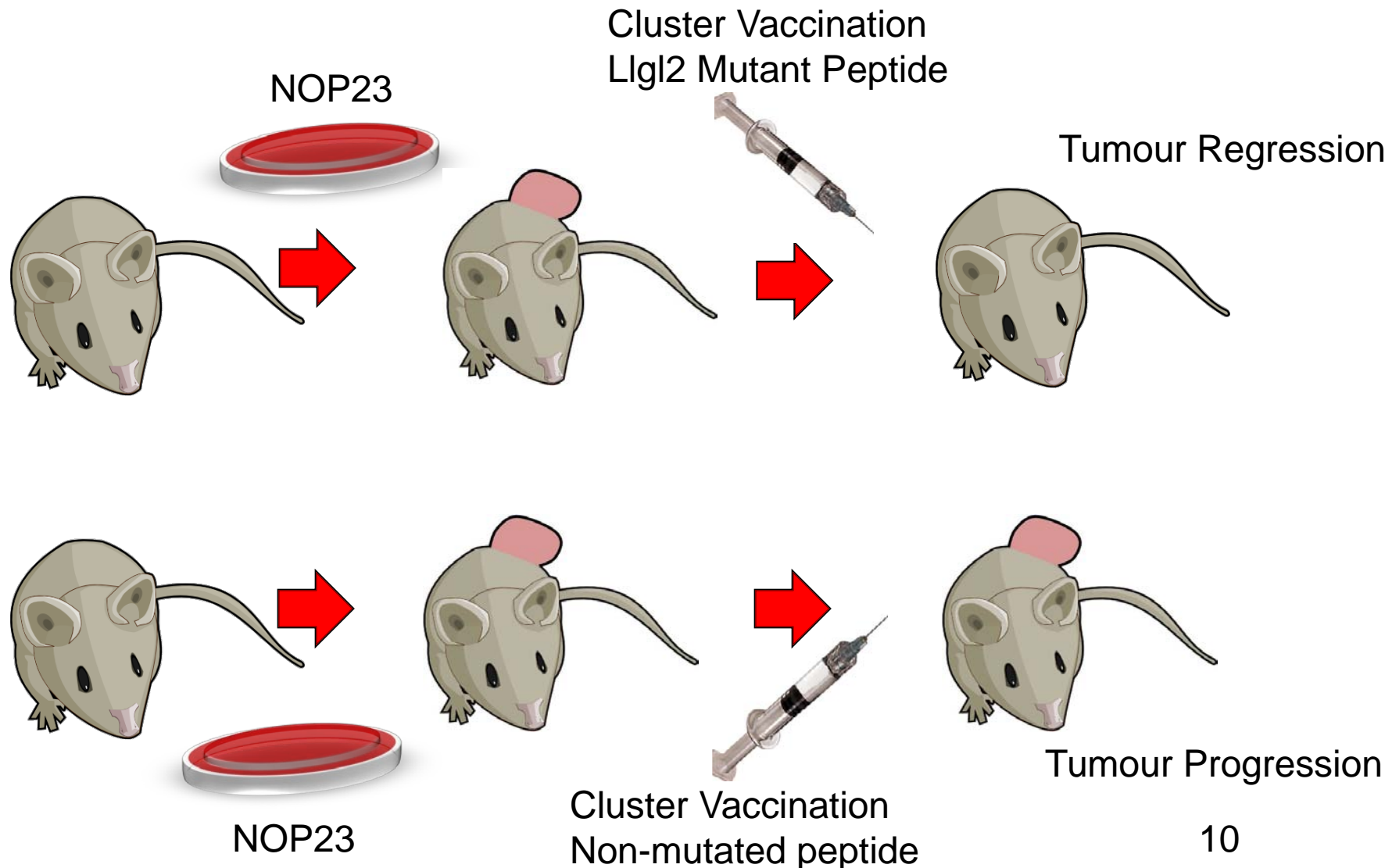
[Control of tumourigenesis by the Scribble/Dlg/Lgl polarity module.](#)

Humbert PO, Grzeschik NA, Brumby AM, Galea R, Elsum I, Richardson HE.
Oncogene. 2008 Nov 24;27(55):6888-907. Review.

[The lethal giant larvae tumour suppressor mutation requires dMyc oncoprotein to promote clonal malignancy.](#)

Froldi F, Ziosi M, Garoia F, Pession A, Grzeschik NA, Bellosta P, Strand D, Richardson HE, Pession A, Grifoni D.
BMC Biol. 2010 Apr 7;8:33.

The Next Experiment: Tumour Regression

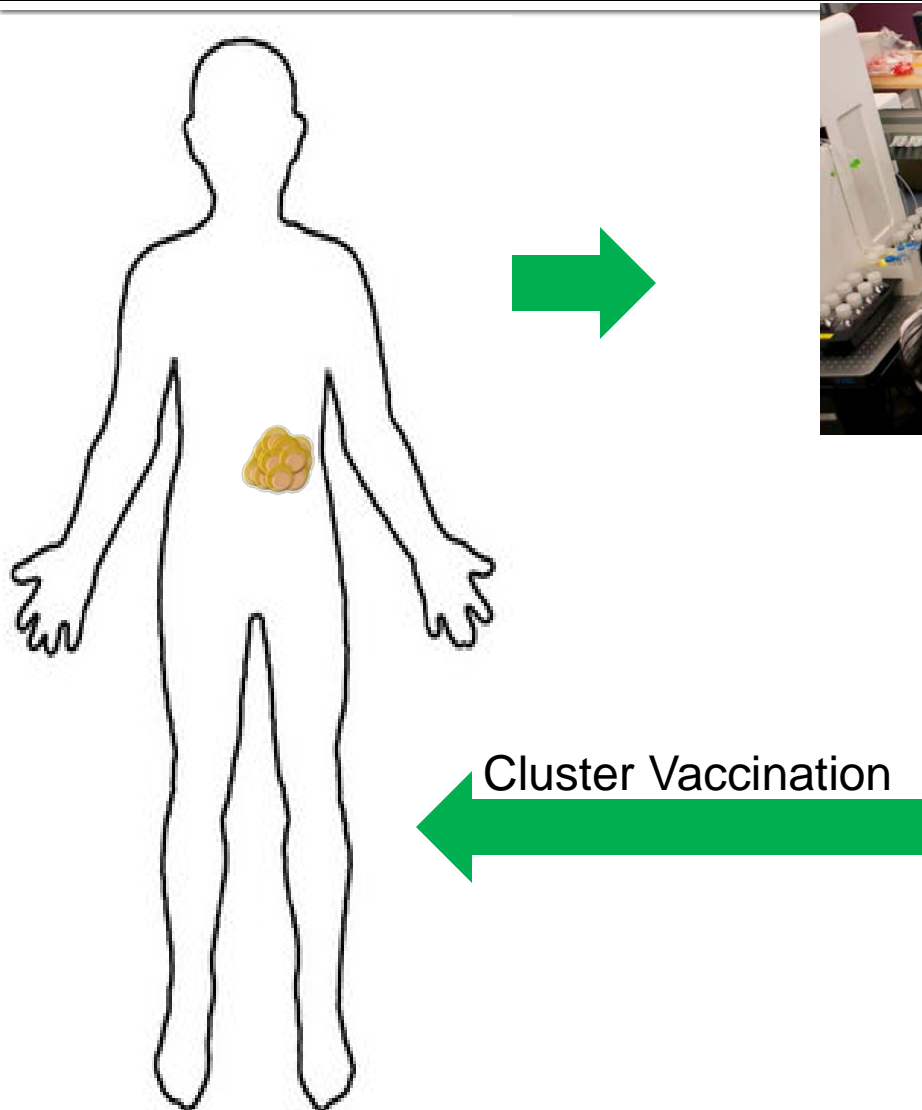


Other NOP Tumour Lines Have Unique Mutational Profiles

Cell Line	NOP20	NOP21	NOP23	NOP13
Missense Point Mutations	Ccdc107	Ppl Axl Acbg1	Llgl2 Bicd2 Arid5a Mtap7d1	Lama4 Birc6 Cyp51 Fkbp8 Prkaca Crtap
Fusion Transcripts	p53:Pcbp4	p53:Pcbp4 Tbk1:B4galnt1 (Inversion)	p53:Pcbp4 Errfi1:Clip2 (translocation)	Currantion Ongoing

- Create different tumour specific vaccines for each tumour line
- Use these to activate a T cell response against the unique mutational profile of each tumour line

BCCA is Ideal for Conducting this Type of Clinical Trial



Cluster Vaccination



Acknowledgements

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Dr. Brad Nelson

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