Presenter Disclosure Information

Eric Tran

The following relationships exist related to this presentation:

No Relationships to Disclose

Toward cell transfer immunotherapy against patient-specific mutations in gastrointestinal cancers

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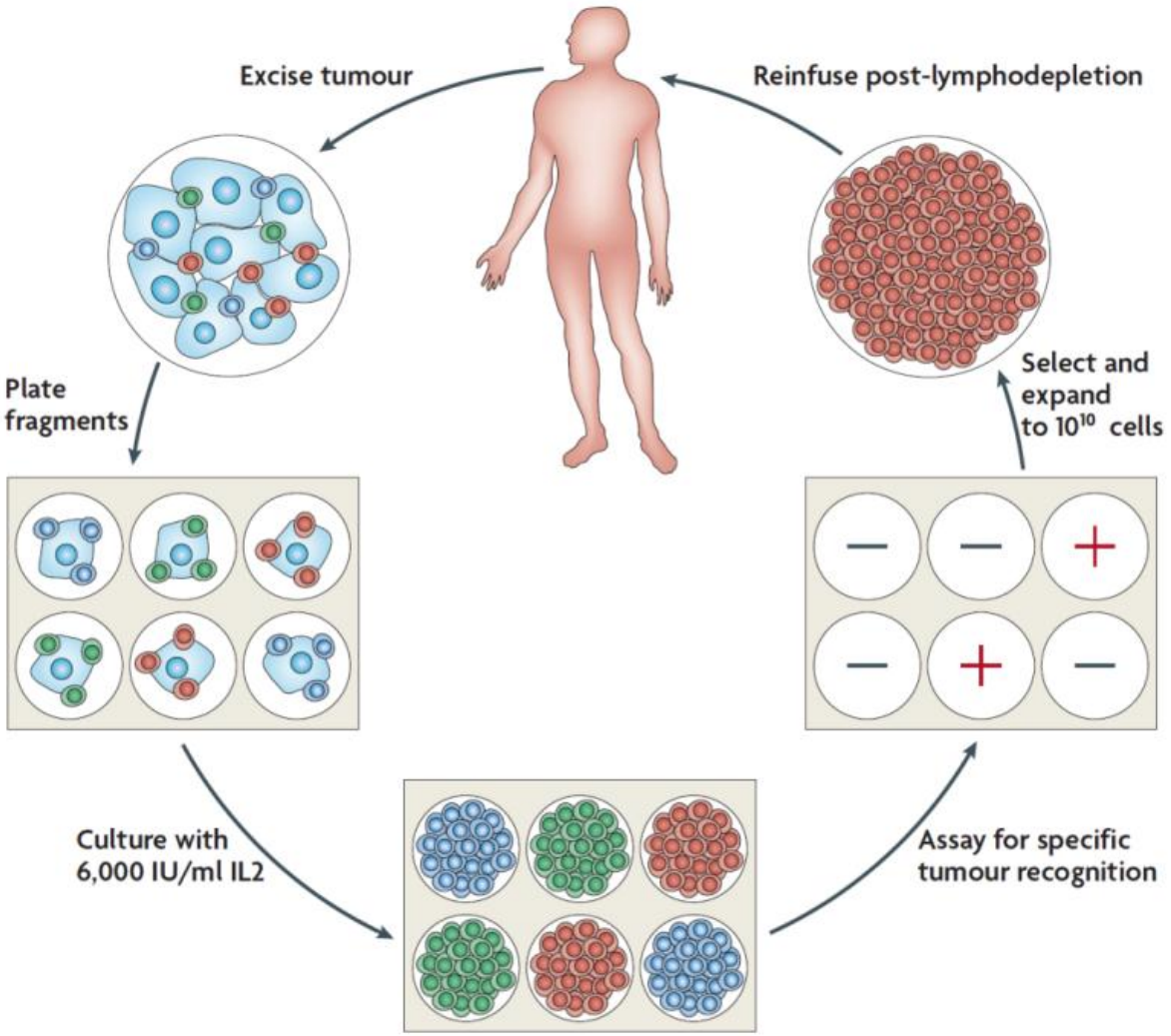
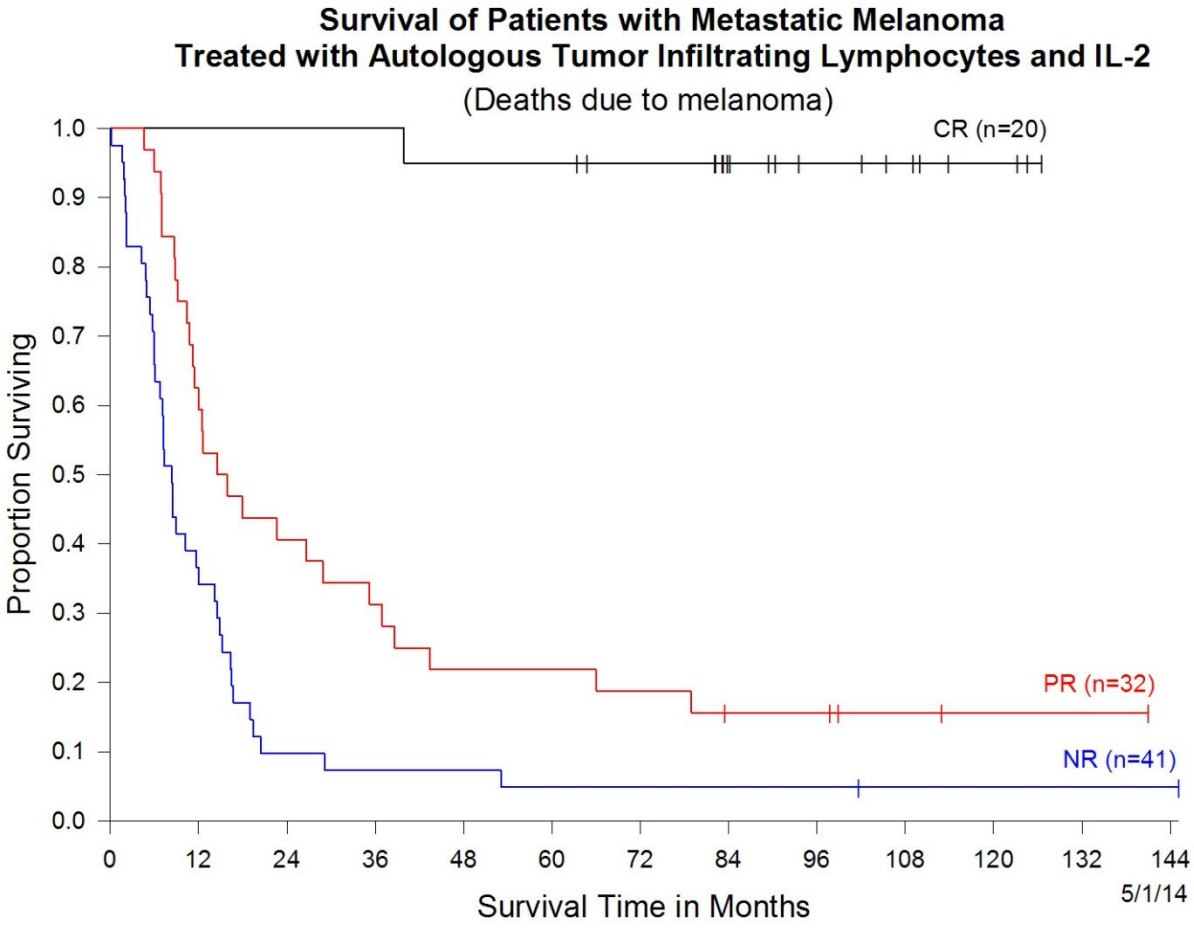
NATIONAL® CANCER INSTITUTE

Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TIL)



Rosenberg SA, et al, Nature Reviews Cancer 8, 299-308 (April 2008)

Adoptive transfer of TIL can cure some patients with metastatic melanoma



Can TIL therapy be effective in other common solid cancers such as gastrointestinal (GI) cancers?

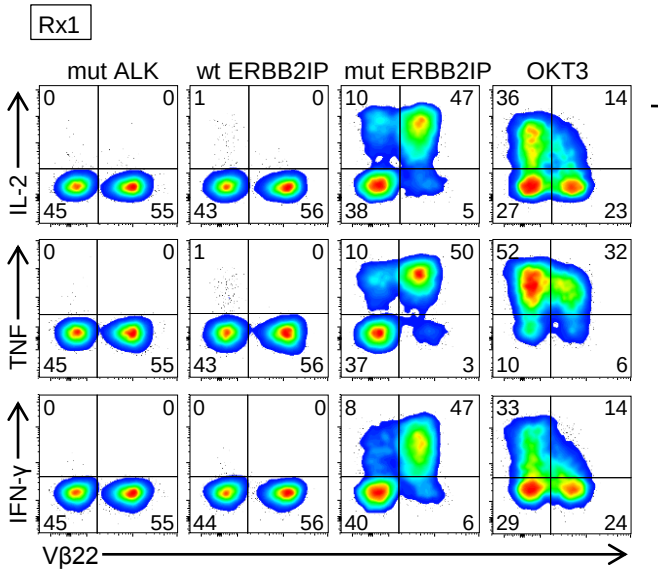
Conventional TIL therapy is largely ineffective against metastatic GI cancers

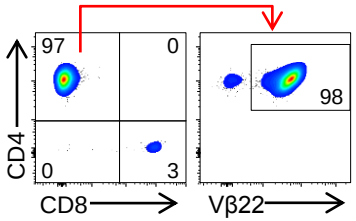
Patient	Primary	Cells ($x10^9$)	IL-2 doses	Response
3454	Colorectal	18.5	8	PD
3596	Colon	32.1	10	PD
3610	Rectal	20.0	3	PD
3671	Colon	30.3	3	PD
3674	Colorectal	69.5	1	PD
3690	Colon	50.0	7	PD
3717	Gastric	68.8	0	PD
3737	Cholangio	42.4	4	PD (13 mo SD)
3788	GE junction	98.1	3	PD
3812	Cholangio	45.2	3	PD
3894	Colon	67.8	3	PD
3942	Rectal	68.3	2	PD
3948	Esophageal	97.3	2	PR (unconfirmed)
3970	Colon (Lynch)	90	2	not evaluable
3971	Colon	40.8	4	PD
3978	Cholangio	78.5	4	PD

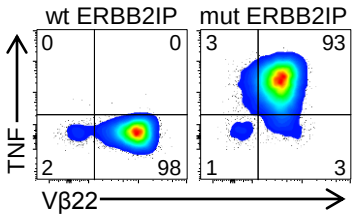
PD: progressive disease
SD: stable disease
PR: partial response

Mutation-reactive T cells can be found in a patient with cholangiocarcinoma and appear capable of mediating tumor regression

ERBB2IP mutation-reactive Vβ22+ Th1 CD4+ T cells detected in TIL of cholangiocarcinoma patient

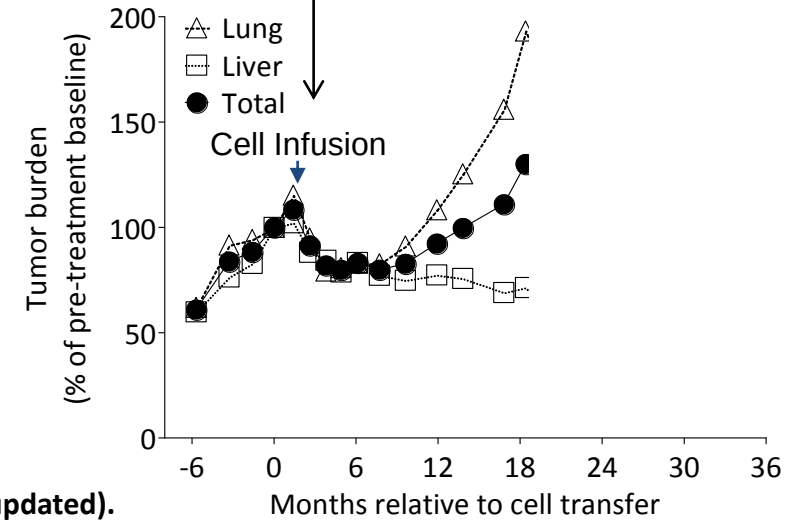






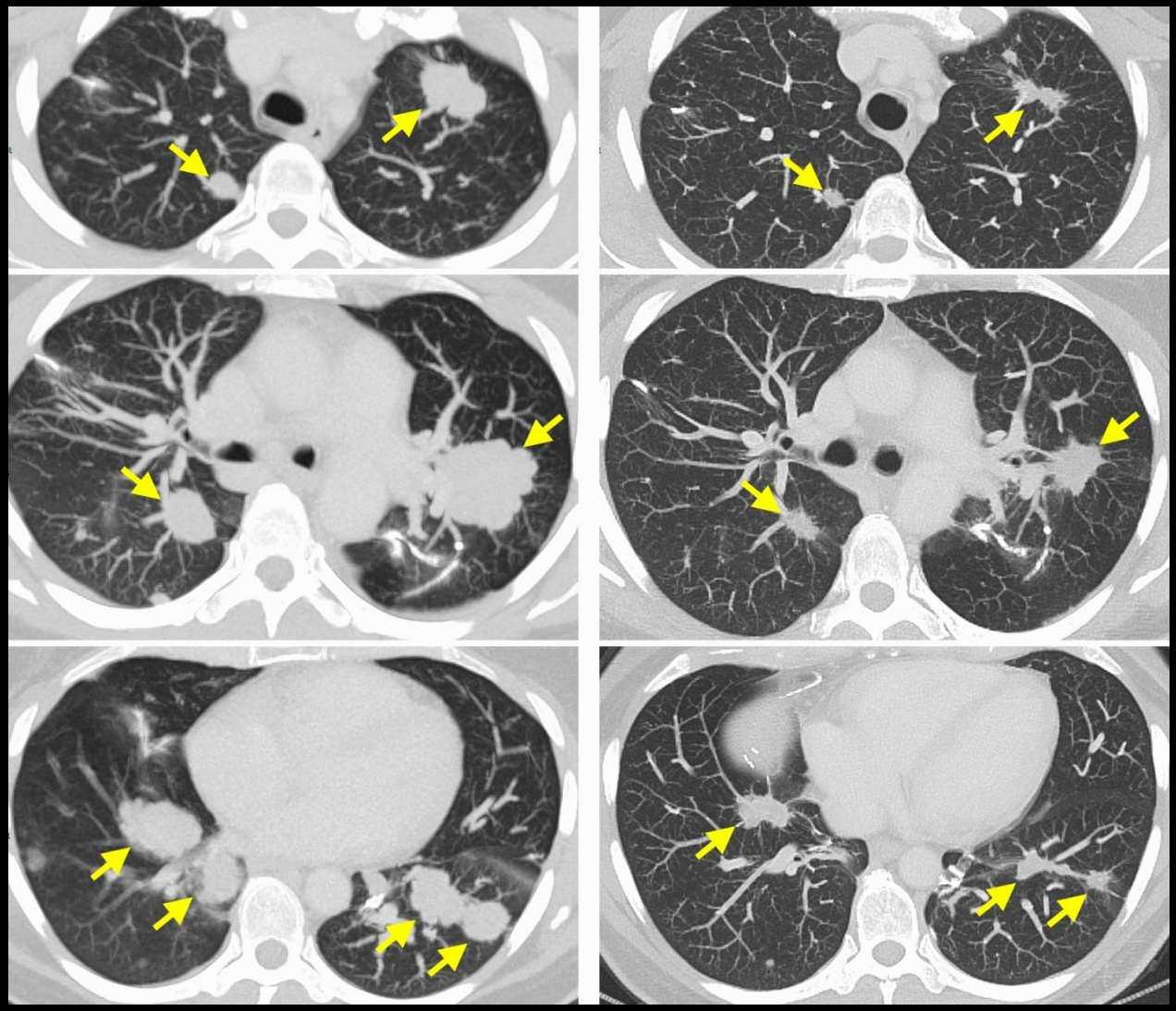
Retreated with ~ 120 billion mutation-reactive Vβ22+ Th1 cells (~ 95% of Rx2)

ACT of > 10 billion mutation-reactive Th1 cells (~25% of Rx1)



Tumor regression after ACT of ERBB2IP-mutation-reactive Th1 cells

Lung CT

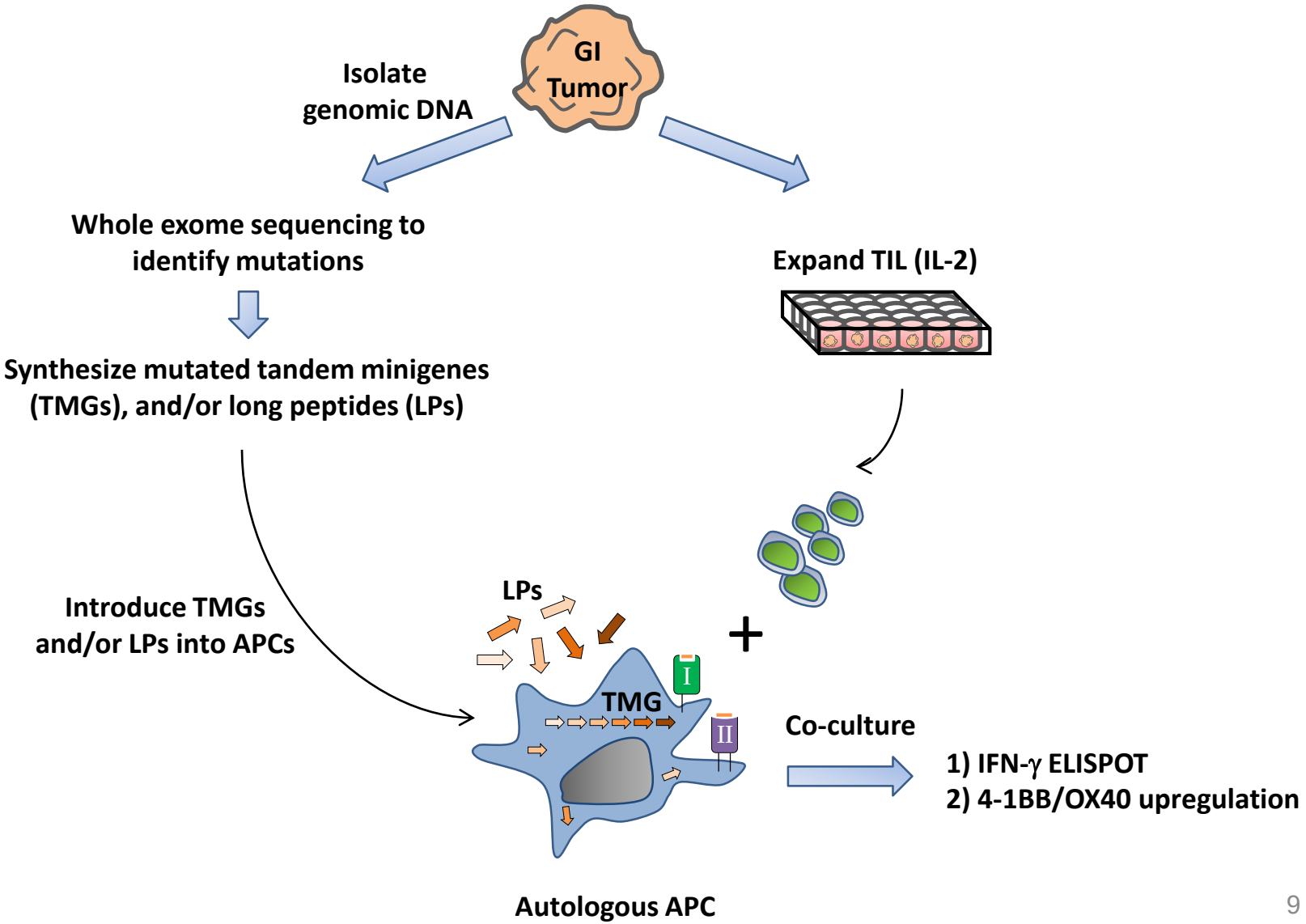


Main Questions and Goal

1. **Are mutation-reactive T cells frequently found in patients with metastatic GI cancers?**

2. **Can we effectively harness the mutation-specific T-cell response to treat patients with GI cancers?**

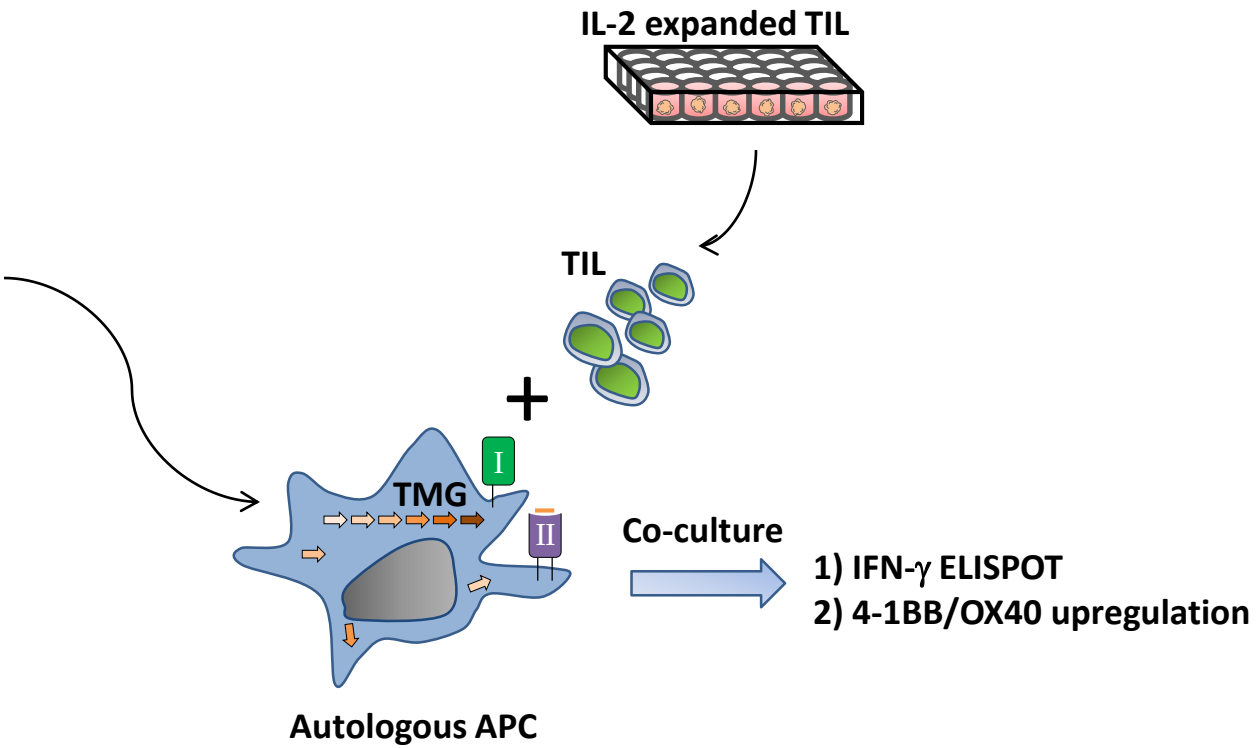
Assessing T-cell reactivity against mutated antigens



Representative example: metastatic colorectal cancer

- 52-year old male with primary colon cancer metastatic to the liver and lung
- Hepatic wedge resection for GI-TIL and whole exome sequencing
- 134 mutations (PGDx, stringent), 300 mutations (in-house, relaxed)
  - 17 TMGs constructed

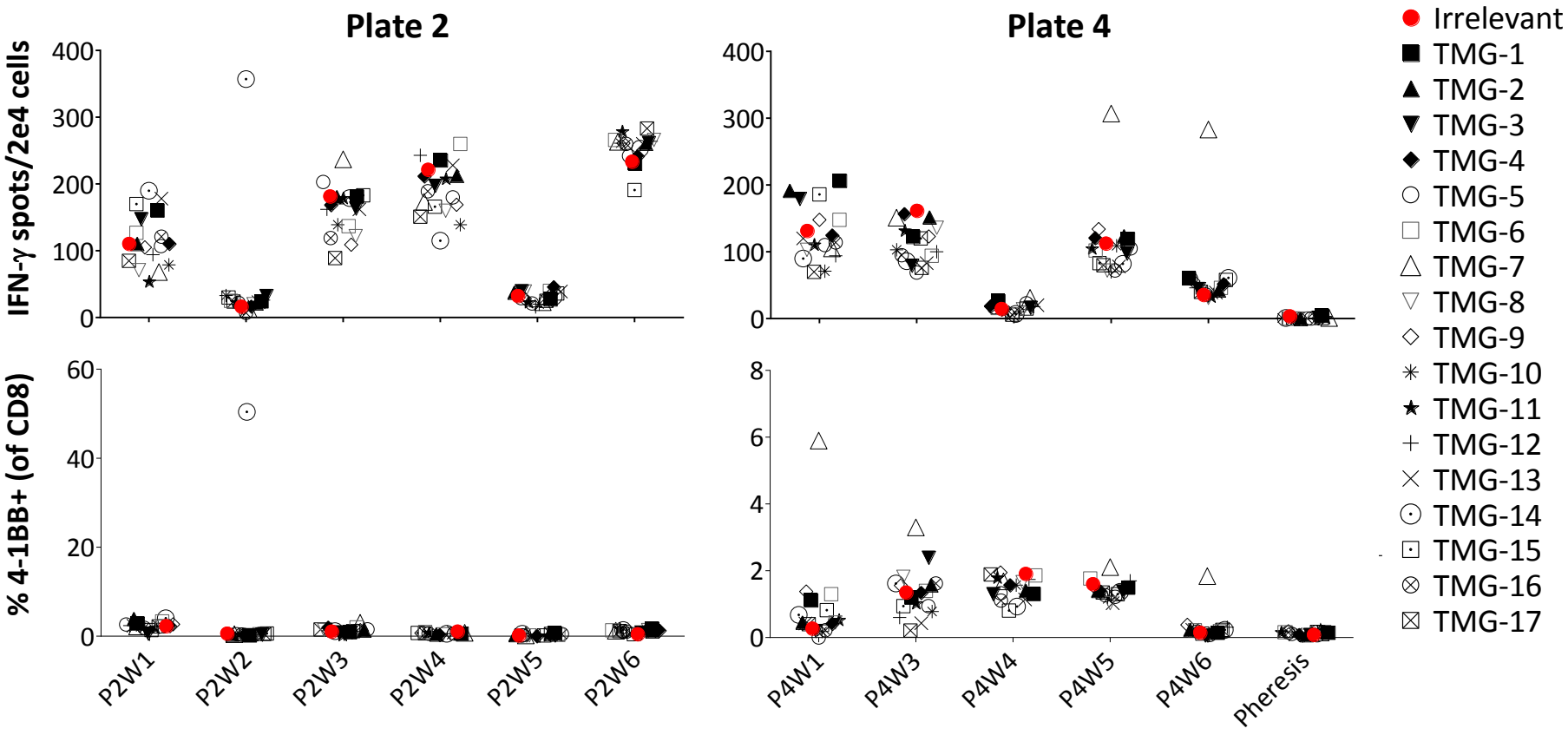
TMG	# minigenes
1	16
2	16
3	16
4	16
5	16
6	16
7	16
8	12
9	16
10	15
11	16
12	14
13	16
14	16
15	16
16	16
17	15



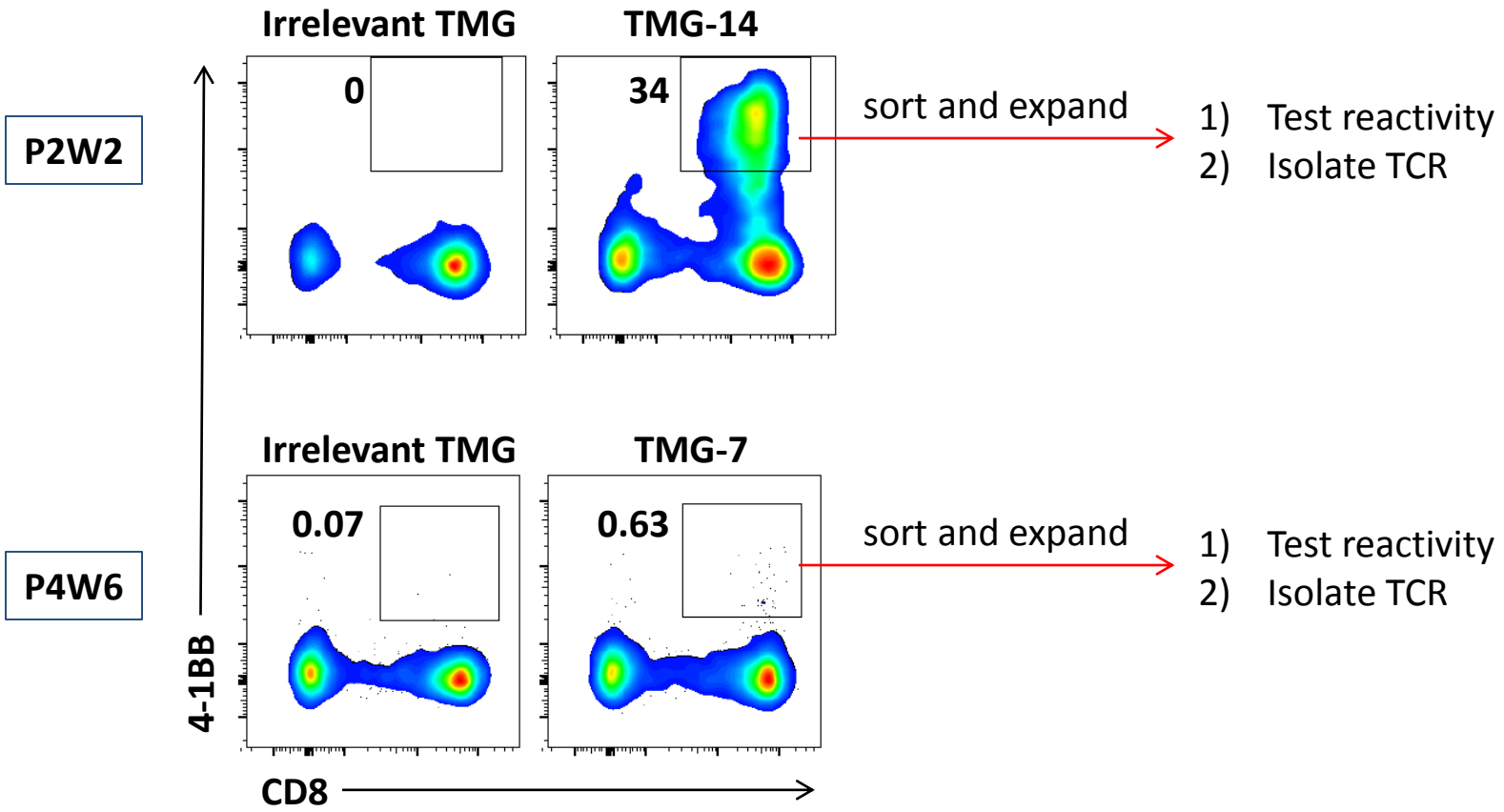
Several TIL cultures display reactivity against TMG-7 and TMG-14

Co-culture: TIL fragments with TMG RNA transfected DCs (2/4 plates shown)

IFN-γ ELISPOT (top); 4-1BB upregulation by flow cytometry (bottom)



Enrichment of TMG-7 and TMG-14 reactive T cells

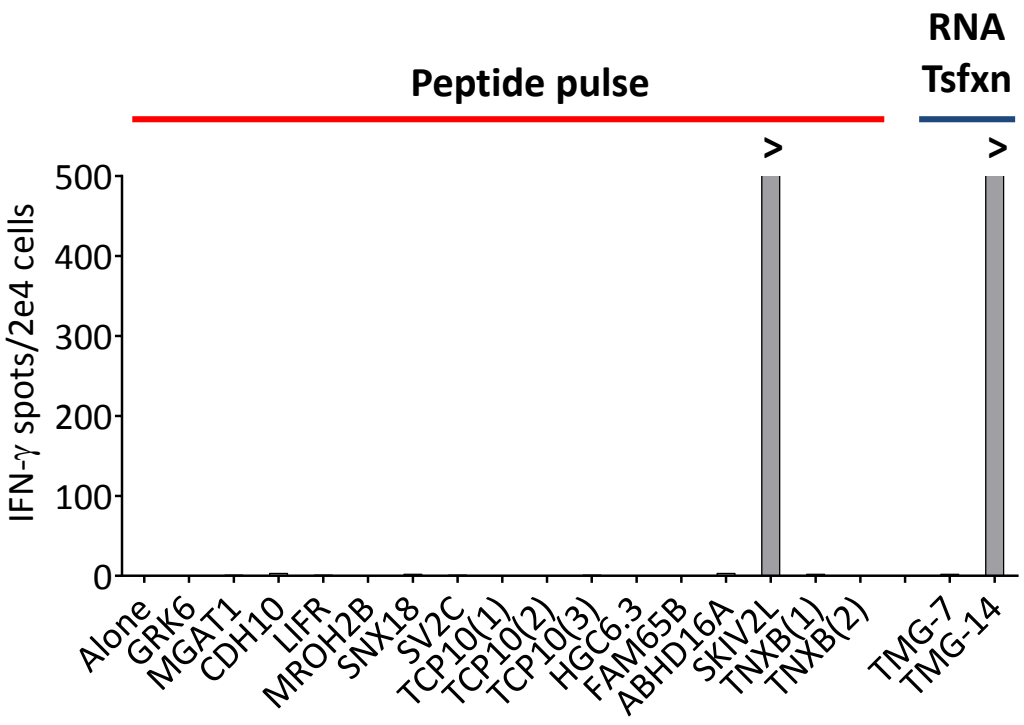


TIL from P2W2 recognize mutated SKIV2L

Co-culture: P2W2 sorted T cells + DCs pulsed with long peptides or transfected with TMG RNA

TMG-14

Mutated gene	Long peptide AA sequence
GRK6	CRGGSAREVKEHRLFKKLNFKRLGA
MGAT1	PGRPPSVSALDGAPASLTREVIRLA
CDH10	TTVNITLTDVNDKPPRFPQNTIHLR
LIFR	VIVGVVTSILCYQKREWIKETFYPD
MROH2B	LWDPNPKIGVACHDVLMVCIPFLGL
SNX18	YSTGEEASRDVDTWVFSLECKLDCS
SV2C	MEYDNGRFIGVKLKSVTFKDSVFKS
TCP10(1)	AFGKISHLSADEETTPKYAGRKSQS
TCP10(2)	TLALEPAFGKISPLSADEETTPKYAGRKSQS
TCP10(3)	LLALEPAFGKISPLSADEDTTPKYA
HGC6.3	VFSSPHTAGGMTSTVFSSPHTAGGM
FAM65B	MSDLAPSNLLAQHEVLRTLALLLTR
ABHD16A	NEIDTMFVDRRGAAEPQGQKLVICC
SKIV2L	PILKEIVEMLFSHGLVKVLFATETF
TNXB(1)	RETSAKVNWMPPRSRADSFKVSYQL
TNXB(2)	QFIPTASPLLCSSSPHSPAKAEAEI



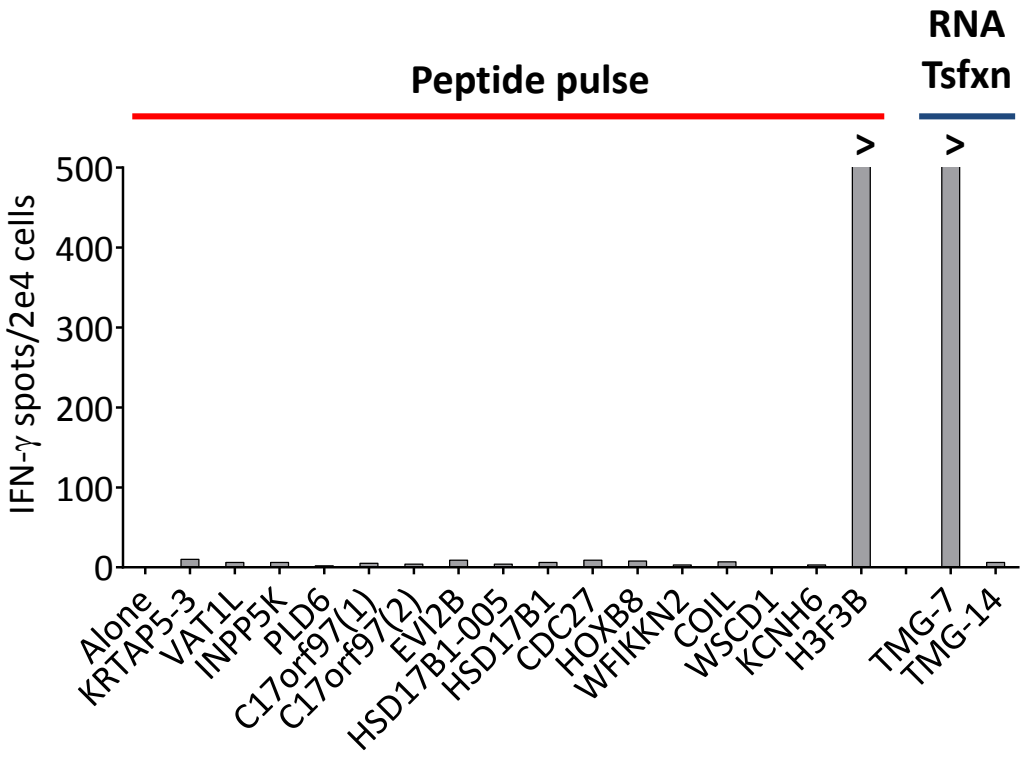
SKIV2L: putative RNA helicase involved with altering RNA secondary structure

TIL from P4W6 recognize mutated H3F3B

Co-culture: P4W6 sorted T cells + DCs pulsed with long peptides or transfected with TMG RNA

TMG-7

Mutated gene	Long peptide AA sequence
KRTAP5-3	CGSCGGCKGGCGACGGSKGGCGSSC
VAT1L	IDNPPKTPLVPGYECSGIVEALGDS
INPP5K	PAWTDRILWRLKQQPCAGPDTPIPP
PLD6	DCDYMALNGSQIRLLRKAGIQVRHD
C17orf97(1)	RLDRRGGAGTMGDKDNDGEEEEREG
C17orf97(2)	FHIDPEALKGFHTDPKALKGFHPDP
EVI2B	TSTVKNSPRSTPPRSTPGFILDTTSNKQTP
HSD17B1-005	RRGSGRVLVTGSLGGLMA
HSD17B1	RRGSGRVLVTGSLGGLMGLPFNDVY
CDC27	LNTDSSVSYIDSA
HOXB8	PSSGGSFQHPSQTQEFYHGPSSLST
WFIKKN2	DRENVVMRPNHVCGNVVVTNIAQLV
COIL	NKATCGTVGDDNKEAKRKSPKKKEK
WSCD1	TICVKTHESGRRGIEMFDSAILLIR
KCNH6	VAAIPFDLLIFRNGSDETTTLIGLL
H3F3B	VKKPHRYRPGTVTLREIRRYQKSTE



H3F3B: histone protein of the H3 family

Mutation-reactive TIL identified in 7 out of 8 patients with metastatic gastrointestinal cancers

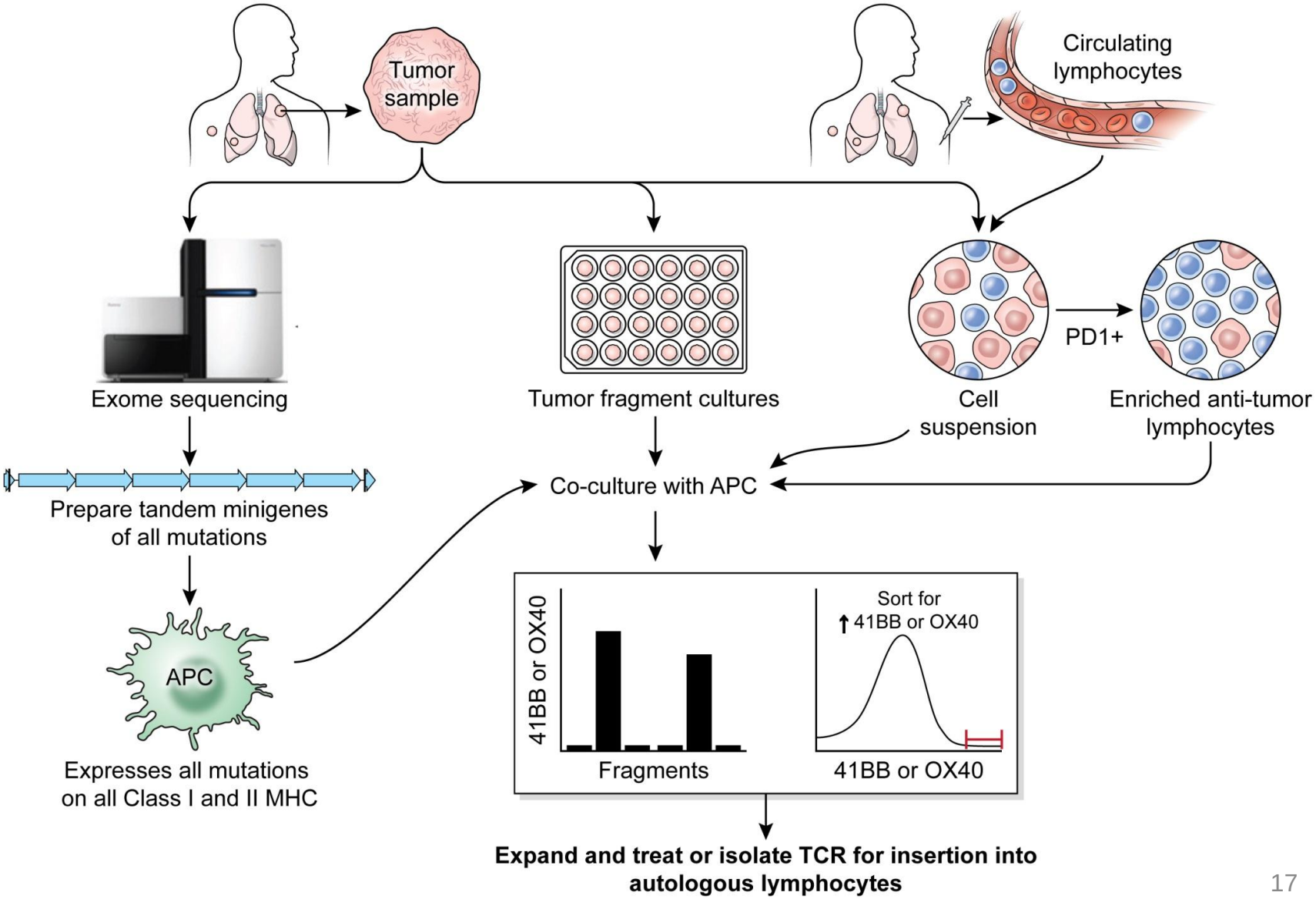
Patient	Cancer	# of mutations assessed	Mutation Reactive T cells?	Mutated gene recognized	T cell	Notes
3737	Cholangio	25	Y	ERBB2IP	CD4	Multiple clonotypes; TCRs isolated
3812	Cholangio	179	N	-------	-------	High background in TIL
3942	Rectal	140	Y	NUP98 KARS GPD2	CD8 CD8 CD4	TCRs isolated
3948	Esophageal	210	Y	PLEC ASTN2	CD4 CD4	
3971	Colon	119	Y	CASP8	CD8	TCR isolated
3978	Cholangio	37	Y	ITGB4	CD4	
3995	Colon	154	Y	in progress	CD8	Potentially 4 reactivities
4007	Colon	265	Y	SKIV2L H3F3B	CD8 CD8	Two clonotypes for SKIV2L; testing TCRs; potential low freq. CD4

Mutation-reactivity is highly heterogeneous between TIL cultures from the same patient

Conclusions

- **Conventional TIL therapy is largely ineffective against metastatic gastrointestinal cancers**
- **Transfer of a highly pure population of mutation-reactive T cells appeared capable of mediating tumor regression in a patient with cholangiocarcinoma (ongoing PR)**
- **Most patients (7/8) with metastatic gastrointestinal cancers appear to mount a T-cell response against at least one somatic mutation expressed by their tumors**
- **Mutation-reactive T cells and their T-cell receptors can be enriched and isolated for potential use in cell-based therapies**

The future of T-cell therapy for common solid cancers?



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