

## 1 **Current Status of T-Cell Adoptive Transfer for Advanced Cancer**

### 2 **Adoptive T-Cell Therapy**

- The goal is to generate the largest number of tumor-reactive T-cells in patients with cancer
- 
- This approach transfers cultured tumor-reactive T-cells, expanded in vitro, into a properly prepared recipient
- 
- Allows manipulation of the host to minimize inhibitory factors and to support the transferred T-cells

### 3 **Adoptive T-Cell Therapy: Two Basic Flavors**

Naturally occurring T-cells: Tumor Infiltrating Lymphocytes (TIL)

- Melanoma

Genetically engineered T-cells: Modifying peripheral blood lymphocytes to introduce new functions and specificities

- Classical MHC-restricted T-cell receptors
- Chimeric (antibody-based) antigen receptors (CARs)

### 4 **Lessons from Melanoma**

- Melanoma is unique in that most patients with melanoma harbor tumor-reactive infiltrating lymphocytes in their metastatic lesions
- These tumor infiltrating lymphocytes (TIL) are a consistent source of T-cells to expand in culture and administer
- Therefore most of the principles known about autologous T-cell transfer were learned from giving TIL to patients with melanoma

### 5 **Melanoma TIL (Tumor Infiltrating Lymphocytes)**

### 6 **TIL History**

- Simply infusing large numbers of TIL expanded in vitro along with supportive IL2 caused a third of patients with metastatic melanoma to respond, but responses were often brief
- Survival of transferred T-cells in vivo was extremely low
- Mouse models showed that efficacy was reduced by:
  - Regulatory (inhibitory) T-cells
  - Low endogenous levels of supportive cytokines
  - Competition for those cytokines by other T-cells

### 7 **Lesson #1**

- Immunosuppressing the host immediately before adoptive T-cell transfer improves survival of transferred cells and increases efficacy
- This is because:

- Endogenous regulatory T-cells are deleted
- Lymphopenia stimulates IL-7 and IL-15 to be produced from non-lymphoid sources to 'restore' lymphocytes to normal
- There are fewer bystander immune cells competing for and consuming those cytokines

8 9 10 11 12 13 14 

15  **TIL Transfer Therapy**  
**(Response Duration- Months)**

Pre-Treatment	Total	PR	CR	OR (%)
Cy/Flu	43 (84, 36, 29, 28, 14, 13, 11, 8	16 8, 7, 4, 3, 3, 2, 2, 2)	5 (95+, 82+, 79+, 78+, 64+)	21 (49%)
C/F + 200 TBI	25 (14, 9, 6, 5, 4, 3, 3)	8 6, 5, 4, 3)	5 6 57+, 54+)	13 (52%)
C/F + 1200TBI	25 (21, 13, 7, 6, 6, 5, 4, 3)	8 6, 5, 4, 3)	10 (48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19)	18 (72%)

16 17 18 

19  **Newer TIL Trials**

- Rapidly growing TIL without in vitro reactivity testing (and treating all patients) is an approach called "Young TIL"
  - Can also cause durable major regressions
  - Marginally lower RR, but much easier

- Other institutions have been able to begin this (Ella Institute, Israel, MDACC, Moffitt Cancer Center)
- Randomized Phase II trial enriching Young TIL for CD8 cells did not improve efficacy

20 21  **Newest TIL Protocol**

- Intensifying preparative host immunosuppression
  - The best outcome in Phase II TIL studies was from adding 1200 cGy TBI (and CD34 ASCS) to Cy-Flu
  - The overall RR was 72% with 40% CRs and only one of these 10 CRs relapsed (all with >4 yrs F/U)
  - Murine models show that intensifying preparative TBI increases ACT efficacy and CD34 BMSC also contribute
- Accruing: Randomized trial of TIL with Cy-Flu versus 1200 TBI + Cy-Flu

22  **Questions**

- What about adoptive therapy for melanoma patients who cannot grow TIL?
- What about adoptive therapy for patients with non-melanoma tumors?

23  **Applying Adoptive Cell Transfer to Other Patients/Cancers**

- Target other cancers which fortuitously express melanoma-associated antigens
- Capture rare T-cells which react with other cancers and clone their T-cell receptors (TCR) for engineering into any patient's T-cells
- Introduce chimeric antigen receptors (CAR) into PBL which bind tumors with antibodies but activate using normal T-cell signaling machinery

24  **T-Cell Gene Engineering**

Redirecting T-Cell Recognition and Improving T-Cell Capabilities

25 26 27 28 29  **F5 High-Avidity Anti-MART1 TCR**30  **F5 High-Avidity Anti-MART-1 TCR**31 32  **NY-ESO-1**

- Tumor-testis antigen originally found in an esophageal cancer
- Expressed in 10-20% of melanomas
- Also found in myeloma and many common adenocarcinomas (eg. breast, pancreas)
- Expressed in 80% of synovial sarcomas
- The TCR from an HLA-A2-restricted T-cell recognizing NY-ESO-1 was cloned

33  **Adoptive Therapy with Gene-Engineered Lymphocytes: Anti-NY-ESO-1 TCR**

- 12 patients with melanoma treated with 11 evaluable
  - 2 CR (15+, 17+ mo)
  - 3PR (8, 4+, 3 mo)
  -
- 6 patients with synovial sarcoma treated with all evaluable
  - 4 PR (14+, 10, 7+, 5 mo)

34  **Gene Therapy with Anti-NY ESO-1 TCR (Melanoma)**

35

36

37  **Patient #6 with Synovial Sarcoma**

38

39

40  **Chimeric Antigen Receptor (CAR)**

41

42

43

44  **B-Cell Lymphoma: Chimeric Receptor Fusing Anti-CD19 and CD3-zeta**

45

46

47  **Summary**

- Three alternative approaches to engineering tumor-reactive T-cells for adoptive therapy have been tested in very early clinical trials and all have shown evidence of anti-tumor activity
  - Cross-targeting melanoma-associated Ags
  - Transducing patient PBL with TCRs raised in HLA-transgenic mice
  - Using MoAb-based chimeric antigen receptors

48  **Future Directions**

- Another protocol using a CAR against VEGF-R2 (KDR) has also started accruing patients
- A protocol to use systemic IL-15 to support T-cell transfer has been approved
- Engineering a T-cell to secrete IL-12 enhances its function in mice (fewer cells are equally effective)

49

50  **Acknowledgements:**

- ① • Mark Dudley
  - TIL Lab
  - Rick Morgan
  - Paul Robbins
  - Marybeth Hughes
  - Udai Kammula
  - Richard Sherry
  - Giao Phan
  - John Wunderlich
  - 
  -
- ② •
  - Dhana Chinnasamy
  - James Kochenderfer
  - Nick Restifo
  - 
  - Clinical Fellows
  - 
  - Nursing Staff (3NW and ACRF3)
  - 
  - 
  - 
  - 
  -