

Simple and Rapid Method for Culture of TILs from Melanoma Tumor Fragments or Core Needle Biopsies of Solid Tumors



As of August 2017, the Moffitt Cancer Center Tumor Infiltrating Lymphocyte (TIL) program had manufactured 45 TIL products for the treatment of melanoma patients. The prerapid expansion (pre-REP) manufacturing process can take 24-38 days to generate a sufficient cell dose for subsequent clinical dose production, during which time the patient is at risk of disease progression and treatment ineligibility. A simplified, rapid method using gas-permeable 24-well culture plates has been developed that decreases the pre-REP from 4 weeks to 3 weeks. The method has also been used to generate TIL cultures from minimally invasive sarcoma core biopsies. As such, unresectable solid tumors such as sarcoma, pancreatic and cervical cancers may now be amenable to TIL therapy.

COMMERCIAL OPPORTUNITY

- The market is attractive as evidenced by about 87 thousand new cases of melanoma in 2017, with metastatic melanoma patients being about 13% of all new cases, or about 10,000 patients a year (ACS; NCI SEER Program). The American Cancer Society predicts that in 2017 there were 12,390 new soft tissue sarcomas diagnosed. Of these sarcomas, it is predicted that a majority will be unresectable. Additionally, there were about 12,820 new uterine cervix cancer cases and 53,670 new pancreatic cancer cases in 2017.
- TIL therapy has been shown to be clinically effective as demonstrated by a 24% Complete Response rate in 101 metastatic melanoma patients by Dr. Steven Rosenberg at the NCI. With a median potential follow-up of 40.9 months, only one of 24 patients who achieved a CR recurred.
- The method is useful for sarcoma patients because a single minimally invasive core biopsy can be used to initiate the TIL culture, rather than conventional methodology that requires a surgical resection as the starting tissue source. This new method has yielded up to 10 times greater TIL number from core biopsy samples compared to fragments in 24-well plates. Additionally, a single core biopsy gives up to 4 times greater yield than fragments grown side by side in gas-permeable culture plates.

TECHNOLOGY

Melanoma tumor fragments (1-3mm³) were cultured in polystyrene or gas-permeable (G-REX, Wilson-Wolf) 24-well culture plates. Each fragment was cultured in a separate well in complete media supplemented with IL-2 (6000 IU/ml) and agonistic anti-41BB antibody (10 µg/ml). TILs cultured in polystyrene plates were re-fed and split upon confluence into secondary 24-well polystyrene plates according to standard protocol and harvested on day 24/25 of culture. TILs cultured in G-REX plates were fed 3X/week, kept in their original wells throughout the culture period and harvested on day 17 or 24. Cell count, viability, immunophenotype, and tumor reactivity were assessed. Sufficient TIL yield for rapid expansion was achieved using a single G-REX well per fragment ($4.4 \times 10^7 \pm 4.3 \times 10^7$, day 17) a full seven days prior to a comparable yield from multiple polystyrene wells ($5.1 \times 10^7 \pm 5.3 \times 10^7$, day 24) ($p=0.32$). TILs grown in G-REX wells showed higher viability (91±3%) on day 17 compared to polystyrene on day 24 (79±5%) ($p<0.000001$). Tumor-specific activity was similar between the two culture conditions, as measured by IFN-γ secretion.

PUBLICATION/PATENT

- Provisional Patent filed on May 5, 2017 for Drs. Kelley, Gerges, Mullinax, Pilon-Thomas, Sarnaik and Hall.

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