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

The Moffitt Cancer Center Tumor Infiltrating Lymphocyte (TIL) program has manufactured 45 TIL products for the treatment of melanoma patients. Currently, the prerapid expansion (pre-REP) manufacturing process takes 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 for sarcoma minimally invasive 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 will be 12,390 new soft tissue sarcomas diagnosed (6,890 cases in males and 5,500 cases in females). Of these sarcomas, it is predicted that 70-75% will be unresectable. Additionally, there will be 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 in a GREX24 plate and can give up to 10 times greater yield than the conventional methodology where there is a surgical resection followed by fragment production, digest and culture of multiple fragments in a single well of a regular 24-well plate. Additionally, a single core biopsy gives up to 4 times greater yield than fragments also grown in GREX24 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 (D) 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 D17/18 or D24/25. 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 (4.4e7±4.3e7, D17/18) a full seven days prior to a comparable yield from multiple polystyrene wells (5.1e7±5.3e7, D24/25) (p=0.32). TIL grown in G-REX wells showed higher viability (91±3%) on D17/18 compared to polystyrene on D24/25 (79±5%) (p<0.000001). Tumor-specific activity was similar, as measured by IFN-γ secretion between the two culture conditions.

PUBLICATION/PATENT

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

CONTACT

Haskell Adler PhD MBA CLP
Senior Licensing Manager
Registered Patent Agent
Haskell.Adler@Moffitt.org
(813) 745-6596

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