TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT IS THE DEFINITION OF TOLERANCE?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• DEFINITION OF TOLERANCE
  – **IMMUNOLOGIC TOLERANCE**: - SPECIFIC IMMUNOLOGIC UNRESPONSIVENESS TO SPECIFIC DONOR TISSUE
  – **OPERATIONAL TOLERANCE**: - LONG-TERM (> 1YR) ALLOGRAFT ACCEPTANCE (CLINICALLY STABLE GRAFT FUNCTION) WITHOUT THE REQUIREMENT FOR CONTINUOUS IMMUNOSUPPRESSION
  – **PROPE TOLERANCE**: “ALMOST TOLERANCE” WHEREBY STABLE ALLOGRAFT FUNCTION IS MAINTAINED BY LOW DOSE NONTOXIC DOSES OF IMMUNOSUPPRESSION WHICH MAY NOT BE REQUIRED INDEFINITELY

CALNE ET AL LANCET 351:1701,1998
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• THE ABILITY TO PRODUCE IMMUNOLOGIC UNRESPONSIVENESS – IMMUNOLOGIC TOLERANCE – WAS FIRST DEMONSTRATED EXPERIMENTALLY BY BILLINGHAM, BRENT & MEDAWAR WHEN THEY SHOWED THAT INNOCULATION OF FETAL MICE OR CHICK EMBRYOS WITH DONOR TISSUE RESULTED IN PERMANENT ACCEPTANCE OF DONOR SKIN ALLOGRAFTS AFTER BIRTH OR HATCHING. THIRD PARTY ALLOGRAFTS WERE REJECTED.

NATURE 172:603, 1953
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHY IS IT IMPORTANT TO ACHIEVE SOME FORM OF TOLERANCE?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• IMPORTANCE OF ACHIEVING TOLERANCE IN SOLID ORGAN ALLOGRAFT RECIPIENTS
  – DESPITE DRAMATIC IMPROVEMENT IN SHORT-TERM RENAL ALLOGRAFT FUNCTION WITH CURRENT IMMUNOSUPPRESSIVE AGENTS LONG-TERM ALLOGRAFT SURVIVAL RATES HAVE IMPROVED MINIMALLY ESPECIALLY RENAL ALLOGRAFTS
  – SIDE EFFECTS FROM IMMUNOSUPPRESSIVE AGENTS PRODUCE SIGNIFICANT MORBIDITY AND ADVERSELY IMPACT ON THE QUALITY OF LIFE AS WELL AS LONG TERM GRAFT AND PATIENT SURVIVAL RATES
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

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DD APPROXIMATING LD SURVIVAL AT 1, 3 YEARS FOR THE MOST RECENT COHORT
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• SIDE EFFECTS FROM IMMUNOSUPPRESSIVE AGENTS
  – MALIGNANCY
  – CARDIOVASCULAR DISEASE
  – NEPHROTOXICITY
  – GROWTH RETARDATION
  – COSMETIC SIDE EFFECTS
  – NON-ADHERENCE
CUMULATIVE INCIDENCE OF CHRONIC RENAL FAILURE AMONG 69,321 PERSONS WHO RECEIVED NONRENAL ORGAN TRANSPLANTS IN THE UNITED STATES 1990-2000

OJO ET AL NEJM SEPT 4, 2003 349:931-940
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• THEREFORE, ACHIEVING PROPE OR CLINICAL OPERATIONAL TOLERANCE (COT) WOULD POTENTIALLY EXTEND ALLOGRAFT LONGEVITY (ALLEVIATE NEPHROTOXICITY) AND MAXIMIZE THE QUALITY OF LIFE OF RECIPIENTS

• IN ADOLESCENTS AND YOUNG ADULTS IT WOULD ALLEVIATE THE IMPACT ON NON-ADHERENCE (NA) ON LONG-TERM ALLOGRAFT FUNCTION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHAT IS THE CURRENT STATUS OF CLINICAL OPERATION TOLERANCE (COT)?

WHAT GROUPS OF SOLID ORGAN TRANSPLANT RECIPIENTS HAVE EXHIBITED COT?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL OPERATIONAL TOLERANCE (*COT*)
  - THOSE WHO EXHIBITED **NON-ADHERENCE** (*NA*) TO IMMUNOSUPPRESSIVE MEDICATIONS
  - THOSE WHO UNDERWENT **PLANNED WEANING** OR DISCONTINUATION OF IMMUNOSUPPRESSIVE MEDICATIONS BECAUSE OF SEVERE TOXICITY OR LIFE-TREATENING COMPLICATIONS (PTLD, INFECTION)
  - **PROTOCOLS** FOR PLANNED WEANING AND EVENTUAL DISCONTINUATION OF ALL IMMUNOSUPPRESSIVE MEDICATIONS IN CLINICALLY STABLE LONG-TERM SURVIVORS (LIVER TRANSPLANT RECIPIENTS)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• CLINICAL OPERATIONAL TOLERANCE (COT)
  - PROTOCOLS COMBINING HEMATOPOETIC CELL AND KIDNEY TRANSPLANTATION FROM THE SAME DONOR WITH NONMYELOABLATIVE CONDITIONING TO ESTABLISH TEMPORARY OR PERSISTENT MIXED CHIMERISM WITH SUBSEQUENT RAPID DISCONTINUATION OF IMMUNOSUPPRESSIVE THERAPY
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT WERE THE DATA DOCUMENTING CLINICAL OPERATIONAL TOLERANCE (COT) IN RENAL ALLOGRAFT RECIPIENTS?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **COT**: NON-ADHERENCE (*RENAL*)
  - ’75 - ’76: INITIAL REPORTS OF 23 NA RECIPIENTS
    - 17 REJECTED
    - 6 HAD “STABLE” GRAFT FUNCTION FOR 17-60 MO.
  - ’75 & ’80: NATIONAL SURVEYS IN UNITED STATES
    - 24 RECIPIENTS OFF IMMUNOSUPPRESSION WITH ONLY 2 SUSTAINED FOR 9 AND 36 MO.
    - 23 RECIPIENTS OFF IMMUNOSUPPRESSION FOR > 8 MO. WITH 6 > 3 YEARS
  - ’96: ONE RECIPIENT WAS NA DURING PREGNANCY AND REMAINED OFF IMMUNOSUPPRESSION FOR 9 YEARS WITH NORMAL ALLOGRAFT FUNCTION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL OPERATIONAL TOLERTANCE (**COT**)
  - ‘06: 10 RECIPIENTS OFF IMMUNOSUPPRESSION FOR 1 TO 20 YEARS (FRANCE)
  - 7 NON-ADHERENT AND 3 PTLD/MALIGNANCY
  - 5 HAD A PRIOR ACUTE REJECTION EPISODE
  - 2 HAD DECLINE IN ALLOGRAFT FUNCTION AFTER 9 AND 13 YEARS OFF IMMUNOSUPPRESSION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL OPERATIONAL TOLERANCE (COT)
  - ‘10 : 11 RECIPIENTS (EUROPEAN CONSORTIUM FOR TOLERANCE – 3 FROM FRANCE)
    - 8 NA, 1 MALIGNANCY, 1 BMT (SAME DONOR), 1 ?
    - 3 < 21 YEARS OLD
    - OFF IMMUNOSUPPRESSION 3 – 21 YEARS
  - ‘10 : 25 RECIPIENTS (AMERICAN NETWORK FOR IMMUNE TOLERANCE)
    - 20 NA, 2 MEDICAL, 3 ?
    - OFF IMMUNOSUPPRESSION 1 - 32 YEARS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT WERE THE DATA DOCUMENTING CLINICAL OPERATIONAL TOLERANCE (COT) IN LIVER TRANSPLANT RECIPIENTS?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• **COT**: NON-ADHERENCE (*LIVER*)
  - 5 RECIPIENTS 12 1/2 - 18 2/3 YEARS POST – TRANSPLANT WHO WERE OFF IS FOR 5 - 11 YEARS.
  - ALL HAD DONOR MICROCHIMERISM (STARZL: HEPATOLOGY 17:1127, 1993)
    - ONE DIED IN A VEHICULAR ACCIDENT
    - ONE WAS RETRANSPLANTED WITH CHRONIC HEPATITIS C INFECTION 9 YEARS OFF IMMUNOSUPPRESSION
    - 3/5 HAVE NORMAL ALLOGRAFT FUNCTION 14 - 17 YEARS OFF IMMUNOSUPPRESSION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

IS THERE A *SIGNATURE BIOMARKER* THAT CAN IDENTIFY THE RECIPIENT WITH CLINICAL OPERATION TOLERANCE *(COT)*?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- NEWELL (JCI 120:1836,’10)
  - 25 RECIPIENTS WITH COT OFF IS 1 -32 YEARS (US NETWORK OF IMMUNE TOLERANCE)
  - COMPARED GENE EXPRESSION PROFILES AND PERIPHERAL BLOOD LYMPHOCYTE SUBSETS OF TOLERANT RECIPIENTS WITH THOSE RECEIVING IS DRUGS AND HEALTHY CONTROLS
  - TOLERANT GROUP HAD B CELL SIGNATURE WITH UPREGULATION OF CD20 mRNA IN URINE CELLS
  - 3 B CELL DIFFERENTIATION GENES DISTINGUISHED TOLERANT FROM NON-TOLERANT RECIPIENTS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

DO LIVER TRANSPLANT RECIPIENTS WITH CLINICAL OPERATIONAL TOLERANCE (COT) HAVE A DISTINCT BIOMARKER PROFILE?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• PROFILING OF COT LIVER RECIPIENTS
  – 17 COT; 21 NON-COT; 16 HEALTHY CONTROLS
  – MICROARRAYS/REAL-TIME PCR IDENTIFIED GENE SIGNATURES (T CELLS) DISCRIMINATING COT AND NON-COT RECIPIENTS WITH ACCURACY
  – PERIPHERAL BLOOD LYMPHOCYTE PROFILING IDENTIFIED TOLERANCE ASSOCIATED TRANSCRIPTIONAL PATTERNS

MARTINEZ-LLORDELLA ET AL JCI 118:2545, 2008
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• DO THE MICROARRAY AND REAL-TIME PCR GENE EXPRESSION AND PERIPHERAL BLOOD IMMUNOTYPING OR BIOMARKER IDENTIFICATION PROVIDE A “FINGERPRINT” THAT IS SIMILAR IN LIVER AND KIDNEY OPERATIONALLY TOLERANT RECIPIENTS?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- **LOZANO ET AL** *AJT* 11:1916, 2011

  - **RECIPIENTS STUDIED**
    - **KIDNEY** (N=12) - STABLE OFF IMMUNOSUPPRESSION 2 - 13 YEARS
    - **KIDNEY** (N=12) - STABLE IMMUNOSUPPRESSION > 3 YEARS
    - **KIDNEY** (N=12) - CAN WITH C4d DEPOSITS AND DSA
    - **LIVER** (N=12) - STABLE OFF IMMUNOSUPPRESSION 1 - 2 ½ YEARS PER WEANING PROTOCOL
    - **LIVER** (N=12) - STABLE ON IMMUNOSUPPRESSION > 3 YEARS FOLLOWING FAILURE OF WEANING PROTOCOLS
    - **HEALTHY VOLUNTEERS** (N=12)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

  - LIVER AND KIDNEY TOLERANT RECIPIENTS differed from both non-tolerant recipients and healthy volunteers in transcriptional gene expression profiles.
  - Minimal overlap in liver and kidney tolerant related gene expression datasets.
  - Tolerant kidney recipients exhibited peripheral blood B-cell phenotypic markers which were not present in tolerant liver recipients.
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT IS THE CURRENT STATUS OF **BIOMARKERS** (IDENTIFY **GENES** BY MICROARRAY TRANSCRIPTIONAL PROFILING AND VALIDATED BY A qPCR TRANSCRIPTIONAL PLATFORM UTILIZING PERIPHERAL BLOOD MONONUCLEAR CELLS) TO ACCURATELY SEPARATE POTENTIALLY CLINICALLY OPERATIONALLY TOLERANT RECIPIENTS FROM NON-TOLERANT RECIPIENTS OF LIVER/KIDNEY ALLOGRAFTS? (**LONDOÑO ET AL** AJT 12:1370,2012)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- NATURAL KILLER (NK) CELL TRANSCRIPTS MOST ROBUST MARKERS IN LIVER TRANSPLANT RECIPIENTS WITH COT
- “B” CELL GENE EXPRESSION MOST ROBUST IN KIDNEY TRANSPLANT RECIPIENTS WITH COT
- TISSUE GENES INVOLVED IN IRON HOMEOSTASIS IN LIVER TRANSPLANT RECIPIENTS PRIOR TO TRANSPLANTATION (BOHNE ET AL JCI 122:368, 2012)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- THEREFORE, AT PRESENT THERE IS **NO** ROBUST **BIOMARKER FINGERPRINT** THAT CAN IDENTIFY THE POTENTIAL RECIPIENT WHO MAY MANIFEST CLINICAL OPERATIONAL TOLERANCE?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHAT ARE THE DATA FROM PROSPECTIVE WEANING PROTOCOLS IN PEDIATRIC LIVER ALLOGRAFT RECIPIENTS?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• KYOTO EXPERIENCE (‘90 – ’08) (LIVING RELATED DONORS)
  – 200 - WEANING ATTEMPTED
    ❖ 154 - ELECTIVE
    ❖ 48 - NON-ELECTIVE (NA, PTLD, INFECTION)
  – 84 - SUCCESSFUL (15% OF TOTAL TRANSPLANTED)
  – 50 - UNSUCCESSFUL
    ❖ 24 - REJECTED
    ❖ 26 - FIBROSIS ON BIOPSY
  – 66 - UNDERGOING WEANING PROCESS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• KYOTO EXPERIENCE (‘90 – “08) (LRD’s)
  – 50% OF TOLERANT RECIPIENTS EXHIBITED ALLOGRAFT FIBROSIS DESPITE NORMAL LIVER FUNCTION TESTS
  – REINTRODUCTION OF IMMUNOSUPPRESSION LEAD TO REDUCTION IN FIBROSIS IN 50% OF THE TOLERANT RECIPIENTS

OHE ET EL TRANSPLANTATION 90:325, 2010
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• IMMUNE TOLERANCE NETWORK/NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE (USA) FUNDED TRIAL IN 2 CENTERS

• 20 STABLE PEDIATRIC LIVING RELATED DONOR LIVER TRANSPLANT RECIPIENTS HAD IMMUNOSUPPRESSION WITHDRAWN OVER 36 WEEKS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• PARENTAL LIVING DONOR TRANSPLANT

• <18 YEARS OLD AT TIME OF TRANSPLANT

• ≥4 YEARS SINCE TRANSPLANT

• SCREENING LIVER BIOPSY
  – NO ACUTE OR CHRONIC REJECTION
  – FIBROSIS < STAGE 2 (ISHAK)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION:
CONTRAINDICATIONS

• AUTOIMMUNE LIVER DISEASE: AIH / PBC / PSC
• HEPATITIS B OR C
• SECOND ORGAN TRANSPLANT
• AST OR ALT >2X ULN
• TOTAL + DIRECT BILIRUBIN & ALK PHOS OR GGT >2X ULN
• EVIDENCE OF AUTOIMMUNITY (IGG; SEROLOGY)
• CHANGE IN LIVER TESTS IN PRECEDING 2 MONTHS
• GFR <40 ML / MIN / 1.73 M²
• RECENT INCREASE IN IMMUNOSUPPRESSION
12 OF 20 PARTICIPANTS MET THE PRIMARY ENDPOINT: OFF IMMUNOSUPPRESSION FOR 29.2 – 49.9 MONTHS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• ADDITIONAL PROTOCOL EXPANDED TO 12 CENTERS AND INCLUDED *DECEASED DONOR* (65%) PEDIATRIC LIVER Tx RECIPIENTS

• 55/88 (62.5%) COMPLETED WITHDRAWL IMMUNOSUPPRESSION AND 43/88 (49%) HAVE REMAINED OF IMMUNOSUPPRESSION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT IS THE CURRENT STATUS OF PLANNED WEANING OF IMMUNOSUPPRESSION IN ADULT LIVER TRANSPLANT RECIPIENTS?

SANCHEZ-FUEYO LIVER TRANSPLANT 17:S69, 2011
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- SUCCESSFUL WEANING OCCURS IN ABOUT 20% OF LIVER TRANSPLANT RECIPIENTS

- THE TRUE INCIDENCE OF POTENTIAL SPONTANEOUS COT IS UNKNOWN

- PREVALENCE OF COT IS INCREASED IN PEDIATRIC RECIPIENTS UNDERGOING TRANSPLANTATION @ <1 YEAR OF AGE AND IN ADULT RECIPIENTS >10 YEARS POST-TRANSPLANT
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- CLINICAL REJECTION DURING WEANING IS MILD AND VERY RESPONSIVE TO TREATMENT WITH INCREASED IMMUNOSUPPRESSION
- COT RECIPIENTS EXHIBIT TRANSCRIPTIONAL PATTERNS IN BOTH BLOOD AND LIVER TISSUE
- THE LONG-TERM REDUCTION IN MORBIDITY AND MORTALITY FOLLOWING WITHDRAWAL OF IMMUNOSUPPRESSION REMAINS UNKOWN

SANchez-FUEYO  LIVER TRANSPLANT 17:S69, 2011
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• ARE THERE ANY CLINICAL PHENOTYPES PREDICTIVE OF **COT**?

  – 33/75 LIVER TRANSPLANT RECIPIENTS >3 YEARS POST-TRANSPLANT HAD STABLE LIVER FUNCTION FOR ONE YEAR FOLLOWING PLANNED WITHDRAWAL OF IMMUNOSUPPRESSIVE TREATMENT

BOHNE ET AL JCI 122:368,2012
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

— **COT** RECIPIENTS COMPARED TO **NON-COT** RECIPIENTS:

- **HAD BEEN TRANSPLANTED FOR A LONGER PERIOD OF TIME** (p <0.0001)
- **WERE OLDER** (p <0.0005)
- **WERE NOT RECEIVING A CALCINEURIN INHIBITOR** (p <0.014)

**BOHNE ET AL JCI 122:368, 2012**
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT ARE REGULATORY “T” CELLS (\textit{Treg})?
  – A DISTINCT “T” CELL POPULATION, PRODUCED IN THE THYMUS, (PREVIOUSLY KNOWN AS SUPPRESSOR “T” CELLS) THAT MODULATE THE IMMUNE SYSTEM, RETAIN SELF-TOLERANCE AND ELIMINATE AUTOIMMUNITY
  – \textit{Treg} MAINTAIN SELF-TOLERANCE AND HOMEOSTASIS BY SUPPRESSING ABERRANT OR EXCESSIVE IMMUNE RESPONSES
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT ARE THE MECHANISMS OF Treg CELL IMMUNOSUPPRESSION?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- SUPPRESS ACTIVITY OF ANTIGEN PRESENTING CELLS (APCs) AND EFFECTOR “T” CELLS (Teff) BY DIRECT CONTACT
- SUPPRESS APCs (DENDRITIC CELLS) FUNCTION AND MATURATION BY SUPPRESSIVE CYTOKINES IL10 AND TGFβ
- DESTROY Teff THROUGH SECRETORY PERFORIN AND GRANZYMME A

HAQUE ET AL FRONTIERS IN ONCOLOGY 4:1, 2014
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT IS THE USUAL NUMBER OF Treg CELLS IN HUMANS?
  — 70 kg YOUNG ADULT HUMAN
    ◆ 460 x 10⁹ LYMPHOCYTES
    ◆ 165 x 10⁹ CD4+ “T” CELLS
    ◆ 13 x 10⁹ Treg CELLS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT CLINICAL STUDIES IN HUMANS HAVE LED TO THE DEVELOPMENT OF PROTOCOLS FOR THE USE OF EX-VIVO EXPANDED Treg CELLS FOR INFUSION FOLLOWING SOLID ORGAN TRANSPLANTATION?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- EX-VIVO EXPANSION OF DONOR $T_{reg}$ TO TREAT CHRONIC GVHD (TRZONKOWSKI ET AL CLINICAL IMMUNOLOGY 133:22, 2009)

- EX-VIVO EXPANSION OF THIRD PARTY UMBILICAL CORD BLOOD (UCB) $T_{reg}$ TO PREVENT GVHD IN RECIPIENTS OF UCB STEM CELL TRANSPLANTS (BRUNSTEIN ET AL BLOOD 117:1061, 2011)

- EX-VIVO EXPANSION OF DONOR $T_{reg}$ FROM HLA-HAPLOIDENTICAL HSCT RECIPIENTS TO PREVENT GVHD (IANNI ET AL BLOOD 117:3921, 2011)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- EX-VIVO EXPANSION OF AUTOLOGOUS Treg IN 10 CHILDREN (8-16 y/o) WITHIN 2 MONTHS OF ONSET OF TYPE 1 DIABETES MELLITUS

- @ 11 MONTHS POST-INFUSION 2 PATIENTS WERE OFF INSULIN AND 8 PATIENTS WERE RECEIVING <0.5 IU/kg OF INSULIN (MAREK-TRZONKOWSKA ET AL PEDIATR DIABETES 14:322, 2013)
WHAT IS THE CURRENT STATUS OF THE USE OF Treg IN CLINICAL SOLID ORGAN TRANSPLANTATION?

- PROTOCOLS ARE IN PLACE TO USE EX-VIVO EXPANDED AUTOLOGOUS Treg AS WELL AS DONOR ALLOANTIGEN-REACTIVE Treg (darTreg) IN LIVER AND KIDNEY TRANSPLANTATION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT ARE THE DATA DEMONSTRATING THE ABILITY TO ACHIEVE CLINICAL OPERATIONAL TOLERANCE IN LIVER TRANSPLANT RECIPIENTS WITH EXPANDED AUTOLOGOUS $\text{darTregs}$ BASED TREATMENT?

TODO ET AL HEPATOLOGY 2016
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- 10 ADULT LIVING DONOR LIVER TRANSPLANTS
- AUTOLOGOUS EXPANDED *darTregs* FOLLOWING CO-CULTURE WITH IRRADIATED DONOR CELLS
- CYCLOPHOSPHAMIDE (40mg/kg) ON POD 5
- *darTregs* INFUSED ON POD 13
- ↓ IMMUNOSUPPRESSION (STEROIDS AND MMF ↓ @ 1 MO) (↓ TACROLIMUS STARTED @ 6 MONTHS AND COMPLETED @ 18 MO)
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• 7/10 COMPLETED WEANING FROM TACROLIMUS AND ARE *OFF* TACROLIMUS FOR 16 – 33 MONTHS WITH 4 FOR > 24 MONTHS

• 3/10 WITH AUTOIMMUNE LIVER DISEASES DEVELOPED MILD REJECTION AND RESUMED IMMUNOSUPPRESSIVE THERAPY

TODO ET AL HEPATOLOGY 2016
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

WHAT IS THE CURRENT STATUS OF INDUCING TEMPORARY OR PERSISTENT CHIMERISM WITH SAME DONOR KIDNEY AND HEMATOPOETIC CELL TRANSPLANTATION TO FACILITATE RAPID DISCONTINUATION OF ALL IMMUNOSUPPRESSION?
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• KIDNEY AND HEMATOPOETIC CELL Tx
  – 6 PATIENTS WITH MULTIPLE MYELOMA (MM) AND RENAL FAILURE RECEIVED SIMULTANEOUS KIDNEY AND BONE MARROW Tx FROM HLA IDENTICAL DONORS FOLLOWING NONMYELOABLATIVE CONDITIONING
  – 3 RECIPIENTS LOST CHIMERISM BUT KIDNEY FUNCTION WAS ACCEPTABLE (SERUM CREATININE 0.9 – 2.0 mg/dl) OFF IMMUNOSUPPRESSION FOR 1.3 TO > 7 YEARS
  – 3 RESUMED IMMUNOSUPPRESSION FOR GVHD

FUDABA ET AL AJT 6:2121, 2006
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- KIDNEY AND HEMATOPOETIC CELL Tx
  - 5 PATIENTS RECEIVED COMBINED BONE MARROW AND KIDNEY Tx FROM ONE-HAPLOTYPE MISMATCHED LIVE-RELATED DONORS WITH NON-MYELOABLATIVE CONDITIONING
  - TRANSIENT CHIMERISM AND REVERSIBLE CAPILLARY LEAK SYNDROME OCCURRED IN ALL RECEPIENTS
  - IRREVERSIBLE ACUTE HUMORAL REJECTION OCCURRED IN ONE RECIPIENT
  - IMMUNOSUPPRESSION WAS DISCONTINUED IN 4/5 RECEPIENTS @ 9-14 MO. AND RENAL FUNCTION WAS STABLE FOR 2 – 5.3 YEARS

KAWAI ET AL NEJM 358:353, 2008
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- ENGRAFTMENT SYNDROME
  - 10 RECIPIENTS WITH KIDNEY AND BONE MARROW FROM ONE-HAPLOTYPE MISMATCHED PARENT/SIBLING DONOR
  - 9/10 DEVELOPED SEVERE CAPILLARY LEAK SYNDROME (ENGRAFTMENT SYNDROME) @ 10 -16 DAYS POST-Tx CAUSING SIGNIFICANT RENAL DYSFUNCTION
  - 2 ALLOGRAFTS WERE LOST
  - CHIMERISM WAS TRANSIENT AND UNDETECTABLE AFTER DAY 14
  - 8 RECIPIENTS ARE SURVIVING OFF IS 2 MO – 7 YR WITH A SERUM CREATININE OF 1.1 – 2.0 mg/dl
  - ETIOLOGY OF DAMAGE TO ENDOTHELium IS OBSCURE

FARRIS ET AL AJT 11:1464, 2011
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT ARE THE LONG-TERM RESULTS OF THE MGH PROTOCOL OF TRANSPLANTATION OF HLA-MISMATCHED LIVE-REALTED DONOR KIDNEY AND BONE MARROW TRANSPLANTATION WITH SUBSEQUENT DISCONTINUATION OF MAINTENANCE IMMUNOSUPPRESSION (IS)?

KAWAI ET AL AJT 14:1599, 2014
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

- 7/10 OFF IMMUNOSUPPRESSION >4 YEARS
  - 4/7 OFF IMMUNOSUPPRESSION 4.5-11.4 YEARS
  - 3/7 REINSTITUTION OF IMMUNOSUPPRESSION @ 5-8 YEARS (RECURRENCE OF PRIMARY KIDNEY DISEASE/CHRONIC ANTIBODY MEDIATED REJECTION)
- 3/10 FAILED FROM TMA/REJECTION
- TRANSIENT CHIMERISM ONLY IN ALL RECIPIENTS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• 12/19 (63%) ENROLLED IN RELATED AND UNRELATED LIVING DONOR KIDNEY Tx PLUS FCRx (POD+1) Tx WITH NONMYELOABLATIVE PRE-Tx CONDITIONING ARE CURRENTLY OFF ALL IMMUNOSUPPRESSION FOR 8 TO 48 MO.

• SERUM CREATININE LEVEL 0.79 – 1.54mg/dl

• 2/19 (10.5%) GRAFTS LOST: CNI TMA, INFECTION IN NATIVE PKD

• 11/12 OFF ALL Rx PERSISTENTLY 100% CHIMERIC

LEVENTHAL ET AL TRANSPLANTATION 99:288:, 2015
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• WHAT IS A FACILITATING CELL?
  – 2 PHENOTYPIC POPULATIONS – CD56(bright) AND CD56(neg) THAT PROMOTE HSC ENGRAFTMENT AND HOMING TO FACILITATE CHIMERICISM
  – ESTABLISHMENT OF HIGH LEVELS OF DONOR CHIMERICISM WITHOUT GVHD OR ENGRAFTMENT SYNDROME FOLLOWING NONMYELOABLATIVE CONDITIONING IN MISMATCHED RELATED AND UNRELATED RECIPIENTS

YOLCU ET AL CURR OPIN ORGAN TRANSPLANT 20:57,2015
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• 55 YEAR OLD MALE WHO IS 49 YEARS POST LIVE RELATED KIDNEY TRANSPLANT FROM HIS FATHER. INITIAL IMMUNOSUPPRESSION CONSISTED OF AZATHIOPRINE (IMURAN) 50 mg/DAY AND PREDNISONE 5 mg/DAY. NO CLINICAL REJECTION EPISODES. CURRENT SERUM CREATININE IS 1.7 mg/dl. HE HAS HAD MULTIPLE SKIN CANCERS – BASAL CELL CA, SQUAMOUS CELL CA AND MELANOMA. CURRENTLY ON 100 mg/DAY OF AZATHIOPRINE AND 5mg/DAY OF PREDNISONE.
Kidney Transplant – 1967

Spleenectomy – 1978

Partial left Orichieectomy due to trauma – 1990’s

Basil/Squamous cell carcinoma (left neck) 2003

Melanoma (upper left arm) – 2006

Squamous cell in-situ (right chest) – 2006

Escherichia Coli bacteremia – 2006

Squamous cell/pre/part Aurical Partoid 7-2010

Radiation therapy due to Squamous cell carcinoma Aurical Partoid Oct/Dec-2010

Radiation therapy due to Squamous cell carcinoma Left thumb Dec 2012

Radiation therapy on Right hand above wrist Dec 2012

Osteomyelitis L3-L4 – July/August 2014

Radiation therapy due to Squamous cell on Right Finger March-April 2015

Keratosis’ and squamous cell skin issues continuing
PREDNISONE 5MG TABLETS  1 per day
RAPAMUNE 1MG TABLETS       .5 per day
OMEGA-3 Salmon Oil  1 gm capsule (a.m. and p.m.)
ATORVASTATIN 20 MG TABLET generic for LIPITOR  1 per day (taken at bedtime)
LEVOTHYROXINE 50 MCG tablet 1 tablet per day
ENALAPRIL MALEATE GENERIC FOR VASOTEC  20 MG TABLET 1 Tablet daily
SODIUM BICARB 650 mg one tablet twice a day
CEPHALEXIN GENERIC FOR KEFLEX 500 MG CAPSULE as needed
VITAMIN D 1000 UNIT TAB
Sometimes VITAMIN C
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

IS THIS RECIPIENT CLINICALLY OPERATIONALLY TOLERANT?

WOULD IT HAVE BEEN SAFE TO REDUCE AND/OR ELIMINATE THE AZATHIOPRINE WHICH IN ADDITION TO ULTRA-VIOLET LIGHT IS PRODUCING THE SKIN CANCER?

IF THERE WAS A TEST TO PROFILE THE RECIPIENT WITH COT IT WOULD BE EASIER TO MAKE A DECISION REGARDING DISCONTINUATION OF CURRENT IMMUNOSUPPRESSION!
CONCLUSIONS

– CLINICAL OPERATIONAL TOLERANCE (COT) IS BECOMING A THERAPUETIC REALITY WITH THE IMPLEMENTATION OF PROTOCOLS WHICH FACILITATE WEANING OF IMMUNOSUPPRESSIVE MEDICATIONS @ SOME TIME INTERVAL FOLLOWING TRANSPLANTATION
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

**CONCLUSIONS**

- SUCCESSFUL WEANING IN PEDIATRIC (60%) AND ADULT (20%) LIVER TRANSPLANT RECIPIENTS OCCURS PRIMARALLY IN LONG-TERM (> 3-5 YRS) SURVIVORS WITH EXCELLENT GRAFT FUNCTION

- COMBINED HEMATOPOETIC STEM CELL AND KIDNEY TRANSPLANTATION FROM THE SAME DONOR WITH DEVELOPMENT OF CHIMERISM HAS BEEN SUCCESSFUL IN FACILITATING WEANING IN KIDNEY ALLOGRAFT RECIPIENTS
CONCLUSIONS

THE EMERGENCE OF THE USE OF EXPANDED AUTOLOGOUS Treg CELLS TO FACILITATE WEANING OF IMMUNOSUPPRESSION IN THE EARLY POST-TRANSPLANT PERIOD APPEARS SUCCESSFUL WITH LIMITED SHORT-TERM SIDE EFFECTS ALTHOUGH THERE ARE LIMITED DATA IN LIVER GRAFT RECIPIENTS
TOLERANCE IN SOLID ORGAN TRANSPLANTATION

• **CONCLUSIONS**
  
  – PROFILING OF RECIPIENTS WITH CLINICAL OPERATIONAL TOLERANCE (COT) COULD LEAD TO PROSPECTIVE IDENTIFICATION OF RECIPIENTS WHO CAN SAFELY DISCONTINUE IMMUNOSUPPRESSION
  
  – THE AVAILABILITY OF A SENSITIVE AND SPECIFIC NON-INVASIVE TEST TO DETECT THE POTENTIAL FOR GRAFT REACTIVITY PRIOR TO GRAFT DYSFUNCTION WOULD FACILITATE THE PROCESS OF INDUCING COT