BIOGRAPHICAL SKETCH

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NAME: Richard Paul Junghans

eRA COMMONS USER NAME (credential, e.g., agency login): RPJUNGHANS

POSITION TITLE: President, IT Bio, LLC; Assoc Prof of Medicine, Boston University School of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Harvard College, Cambridge MA	A.B.	1971	Biophysics/ Biochemistry
University of California Berkeley, Berkeley CA	Ph.D.	1975	Molecular Biology
University of Miami, Miami FL	M.D.	1983	Molecular Biology
Georgetown University Hospital, Washington DC	Res/ Fell	1983-86	Internal Med/Hematology
National Cancer Institute, Bethesda MD	Fellowship	1986-91	Medical Oncology

NOTE: The biographical sketch may not exceed five pages. Follow the formats and instructions below.

A. Personal Statement

The projects under this award will involve the application of immune therapies to cancer problems, in basic science, in preclinical development and in clinical translation. I will contribute my 20+ years of experience in laboratory and clinical research in immunotherapies to inform these studies and to advise collaborators in this research program. This experience began with antibodies and their molecular modifications with Dr Thomas Waldmann during my oncology fellowship at the NCI, then extending into my independent research program. I applied my prior PhD training in molecular biology and retroviruses from UC Berkeley to explore genetic modifications to augment and enhance antibody and T cell therapies. I have prepared numerous Phase I-III clinical trial protocols, and I have been sponsor for seven investigator-initiated IND's with release from clinical hold, two with antibody therapies and five with T cell gene therapies. I established and managed two on-campus cell therapy GMP facilities (as Harvard Medical School and Roger Williams Medical Center); I have experience with manufacturing and regulatory aspects relevant to human antibody and cell therapy applications. I have been in drug development for the majority of my career, with basic science, product development, patenting and early Phase clinical trials. I have been a consultant to industry (Genentech, Biogen, Amgen, others) and participated as a consultant in the final FDA approval of a drug I helped to create (daclizumab, Zenopax®, Roche). The usual course of drug development by biotech start-ups is one of acquisition or licensing to big pharma, where the final drug approval process is prosecuted. However, should we retain these agents through to NDA filing, new aspects will undoubtedly be encountered in ushering our own agents to approval and marketing, but I have a degree of comfort with FDA interactions and procedures that will serve the project well. Finally, the work of our team led to the elucidation of pathways for development and expression of exhaustion in normal T cells and CAR-T alike, and novel means for exhaustion's reversal. The IP generated from this work is the founding basis for IT (Immune Therapy) Bio, LLC, and has been back-licensed by IT Bio from the Tufts Medical Center PCT/US17/42147, priority date 7/14/16, inventors Junghans & Balkhi.

Positions and Honors

Positions:

1976-79	Postdoctoral Fellowship, California Institute of Technology, Pasadena CA
1979	Exchange Scientist, U.S.-Japan Cooperative Cancer Program (NCI-Sponsored)
1979-81	Postdoctoral Fellowship, Roche Institute of Molecular Biology, Nutley NJ
1983-86	Residency, Georgetown University Hospital, W ashington DC
1985-86	Fellowship in Hematology, Georgetown University Hospital, W ashington DC
1986-91	Fellowship in Medical Oncology, National Cancer Institute, Bethesda MD
1991-	Director, Biotherapeutics Development Lab
1991-2003	Assistant Professor of Medicine, Harvard Medical School, Boston MA
1995-2003	Member, Gene Therapy Working Group, Harvard Medical School, Boston MA
1996-1998	Immunology Faculty, Harvard Medical School, Boston MA
1996-2003	Asst Professor (adjunct), Bioengineering Program, Boston Univ School of Engineering, Boston

1996-2004	Member, Harvard Institute of Human Genetics, Harvard Medical School, Boston MA
2004-11	Chief, Division of Surgical Research, Roger Williams Medical Center, Providence, RI
2004-present	Associate Professor of Medicine, Boston University School of Medicine, Boston, MA
2014-15	Chief, Section of Hematology, New England Baptist Hospital, Boston, MA
2014-17	Special and Scientific Staff, Tufts Medical Center, Boston, MA
2018-present	President, IT Bio, LLC

Board Certifications: Internal Medicine, Medical Oncology (Board Eligible: Hematology)

Medical Licensure: Massachusetts

Awards and Honors:

1971	*magna cum laude* Award in Biophysics and Biochemistry, Harvard College, Cambridge MA
1977-80	Helen Hay Whitney Postdoctoral Fellowship
1986-87	Chief Fellow, Medicine Branch,National Cancer Institute
1990	Young Investigator Award, American Association of Cancer Research — Upjohn
1993-94	Milheim Foundation Cancer Research Award
1993-96	Clinical Oncology Career Development Award, American Cancer Society
1995	Henry W . Menn Memorial Award, Skin Cancer Foundation
1996-2001	Research Career Development Award (K04), National Cancer Institute
1998-2002	Study Section Member, Cancer Control and Epidemiology, American Cancer Society
2001-2	Vice Chairman, Cancer Control and Epidemiology, American Cancer Society
2003	American Cancer Society Research Scholar
2003-7	Member, Scientific Review Board, National Gene Vector Laboratories, NCRR/NIH
2010	Member, NIH Study Section: Cancer Immunology Immunotherapy (CII)
2010-	Member, NIH Study Section: Clinical Oncology (CONC)

B. Contribution to Science

1. Humanized antibody

I was the point of contact between NIH and Protein Design Labs for the creation of the first humanized antibody in the U.S. and the first to be approved for human use (daclizumab) [a]. I conducted all physicochemical and biological assays of the antibody, helping to shape the final product for human use. I developed a new cell-based assay for assessing antibody affinities that more accurately represents the affinities to be expected on target cells for antibody therapies. I participated in preclinical animal studies [b] and then was PI on clinical studies [c] with this antibody. Applying the then new technique of phage display panning, I directed the identification and characterization of an anti-idiotype antibody in an HTLV-1 patient with adult T cell leukemia (ATL) that expressed CD25 that was speculated by Jerne network hypothesis to inhibit IL2 binding to the leukemic cells to account for his prolonged remission [d]. These studies led the way for many more genetically engineered antibodies that would come to have clinical impact across the spectrum of human disease.

a) **Junghans RP**, Waldmann TA, Landolfi NF, Avdaloric NM, Schneider WP, Queen C. Anti-Tac-H, a humanized antibody that binds to the interleukin-2 receptor: A novel agent for immuno-therapy in malignant and immune disease. Cancer Res 1990;50:1495-502.

b) Brown PS Jr, Parenteau GL, Dirbas FM, Garsia RJ, Goldman CK, Bukowski MA, **Junghans RP**, Queen C, Hakimi J, Benjamin WR, et al. Anti-Tac-H, a humanized antibody to the interleukin 2 receptor, prolongs primate cardiac allograft survival. Proc Natl Acad Sci U S A. 1991;88:2663-7.

c) Koon HB, Severy P, Hagg DS, Butler K, Hill T, Jones AG, Waldman TA, **Junghans RP**. Anti-leukemic effect of daclizumab in CD25 high-expressing leukemias and impact of tumor burden on antibody dosing. Leuk Res 2006;30:190-203.

d) Kingsbury GA, Waldmann TA, **Junghans RP**. Examination of a role for idiotypy in the disease remission of a long term survivor of adult T cell leukemia treated with anti-Tac antibody. Leukemia 1998;12:982-91.

2. Phage display and breast cancer antibody molecular cloning

During a sabbatical at Scripps Research Institute in La Jolla CA with Dr Dennis Burton, I acquired phage display technology, and developed novel methods of cell screening and antigen recovery [a,b]. With this, I was able to identify and clone an anti-idiotype antibody that reacted with a patient's antibody treatment that also suggested elements of reaction against host leukemia antigen [c]. This patient has the longest unmaintained remission of any patient in the history of antibody therapies. Then we turned focus to an important breast cancer problem with identification and cloning of antibodies from plasma cell (PC)-infiltrated tumors that led to improved prognosis. We had to develop procedures for isolating single PCs and then refined PCR procedures for recovery of the VH-VL pairs [d]. We prepared libraries for study of the genes and concluded that >50% of the antibodies in the tumor derived from a few (3-6) originating B cells. This was successful in cloning unique VH+VL antibody pairs [d, e]. To date, this is the only report in the world literature for such unique reagents for probing breast cancer for the neoantigens elaborated.

a) Kingsbury GA, **Junghans RP**. Screening of phage display immunoglobulin libraries by anti-M13 ELISA and whole phage PCR. Nucl Acids Res 1995;23: 2563-4.

b) Watters JM, Telleman P, **Junghans RP**. An optimized method for cell-based phage display panning. Immunotechnology 1997;3:21-9.

c) Kingsbury GA, Waldmann TA, **Junghans RP**. Examination of a role for idiotypy in the disease remission of a long term survivor of adult T cell leukemia treated with anti-Tac antibody. Leukemia 1998;12:982-91.

d) Coronella JA, Telleman P, Truong TT, Ylera F, **Junghans RP**. Amplification of VH and VL (Fab) from single human plasma cells and B cells. Nucleic Acids Res 2000;28:e85.

e) Wang Y, Ylera F, Kang S-G, Kutok JL, Klein-Szanto AJP, Junghans RP. Focused antibody response in plasma cell-infiltrated non-medullary (NOS) breast cancers. Breast Cancer Res Treat. 2007;104:129-44.

3. Systematic assessment of chimeric antigen receptor (CAR) configurations

At the early period of development of so-called "designer" T cells, equipped with chimeric antigen receptors, I evaluated various designs, with Fab or sFv, with or without CD8a hinge spacer [1]. We evaluated two different retroviral vectors (MFG, kat) and 4 different promoters (LTR, CMV, EF1a, SV40). We developed methods for high titer vector producer cell generation [2], and established a GMP facility with new production methods allowing CAR modification of >1e9 cells and expansions to >100 billion cells (1e11). We created TCR-CAR formats that allow that allow interrogation for intracellular antigens for tumor and anti-viral therapies, with unique recombination suppression design that allows both chains in a single vector [3]. We established the critical value of systemic IL2 for optimal activity of dTc against solid tumors in animal studies [4], with strong corroborating data in humans in support of the same conclusion (below).

a) Nolan KF, Yun CO, Akamatsu Y, Beecham EJ, Murphy JC, Leung S, **Junghans RP**. Bypassing immunization: Optimized design of 'designer T cells' against carcinoembryonic antigen (CEA)-expressing tumors, and lack of suppression by soluble CEA. Clin Cancer Res 1999;5:3928-41.

b) Beaudoin EL, Bais AJ, **Junghans RP**. Sorting vector producer cells for high transgene expression increases retroviral titer. J Virological Methods 2008;148:253-9. doi: 10.1016/j.jviromet.2007.12.008.

c) Im EJ, Bais AJ, Yang W, Ma Q, Guo X, Sepe SM, **Junghans RP**. Recombination-deletion between homologous cassettes in retrovirus is suppressed via a strategy of degenerate codon substitution. Mol Ther Methods Clin Dev. 2014;1:14022. PMCID: PMC4239131.

d) Lo ASY, Ma Q, Liu DL, **Junghans RP**. Anti-GD3 chimeric sFv-CD28/T cell receptor zeta designer T cells for treatment of metastatic melanoma and other neuroectodermal tumors. Clin Cancer Res 2010;16:2769-80. doi: 10.1158/1078-0432.CCR-10-0043.

4. Clinical application of designer "CAR" T cells

We were one of the first groups to apply CAR T cells in solid tumors. This was initially with 1st generation anti-CEA designer T cells with doses up to 1e11 T cells [a] that provided data on patient safety and initial indications of response in colorectal, breast and other cancers. This has since expanded to 2nd generation anti-CEA CAR T cells in which a comparison of the impact of IL2 co-administration suggested a validation of the conclusions from animal studies that IL2 is a valuable adjunct for solid tumor treatments [Junghans et al, in process]. We completed a Phase I trial of anti-PSMA CAR T cells in prostate cancer following lymphodepletion conditioning, with engraftments of up to 50% of the host repertoire with the infused T cells [b]. 2/5 subjects met partial response (PR) criteria. Again, response was suggested to be related to adequate systemic levels of IL2 with IL2 infusions. We recently completed a study of hepatic artery infusion (HAI) of CAR T cells, with some activity noted with the IL2 co-administration [c]. I have been a thought leader for safe approaches to CAR T Phase I designs [d], with testimony before FDA and NIH/OBA, and I helped organize an NIH consensus conference on this topic in 2013. An invited commentary on treating solid tumors was recently published [e].

a) **Junghans RP**, Safar M, Huberman MS, Ma Q, Ripley R, Leung S, Beecham EJ. Preclinical and phase I data of anti-CEA "designer T cell" therapy for cancer: A new immunotherapeutic modality. 2001 ASCO Program Proc Abstract #1063.

b) Katz SC, Burga RA, McCormack E, Wang LJ, Mooring JW, Point G, Khare PD, Thorn M, Ma Q, Stainken BF, Assanah EO, Davies RA, Espat NJ, **Junghans RP**. Phase I Hepatic Immunotherapy for Metastases (HITM) study of intra-arterial chimeric antigen receptor modified T cell therapy for CEA+ liver metastases. Clin Cancer Res. 2015;21:3149-59.

c) **Junghans RP**, Ma QZ, Rathore R, Gomes EM, Bais AJ, Lo ASY, Abedi M, Davies RA, Cabral HJ, Al-Homsi AS, Cohen SI. Phase I trial of anti-PSMA designer T cells in prostate cancer: Possible critical role of interacting interleukin 2-T cell pharmacodynamics that determine clinical response in engraftment settings with solid tumor. The Prostate 2016;76:1257-70.

d) **Junghans RP**. Strategy Escalation: An emerging paradigm for safe clinical development of T cell gene therapies. J Transl Med. 2010;8:55.

e) **Junghans RP**. Commentary: The challenges and opportunities of solid tumors for designer CAR-T therapies: A 25-year perspective. Cancer Gene Ther 2017:24:89-99.

5. Elucidation of mechanisms of T cell exhaustion

In an early paper, we noted the failure of IL2 secretion after repeated stimulation of 2nd generation CEA-specific designer CAR-T cells (a). My curiosity about this phenomenon led to repeated testing in my group, and then ultimately was applied as an entrez to the exhaustion phenomenon as this became a prominent clinical concern. This work evolved with two further publications (b, c), in which the latter led to a new elucidation of the pathways for development and expression of T cell exhaustion, and novel means for its reversal. The IP generated from this work is the founding basis for IT (Immune Therapy) Bio, LLC.

a) Emtage PCR, Lo ASY, Gomes EM, Liu DL, Gonzalo-Daganzo R, **Junghans RP**. 2nd generation anti-CEA designer T cells resist activation-induced cell death, proliferate on tumor contact, secrete cytokines and exhibit superior anti-tumor activity in vivo: a preclinical evaluation. Clin Cancer Res 2008;14:8112-22.

b) Balkhi MY, Ma Q, Ahmad S, **Junghans RP**. T cell exhaustion and interleukin 2 downregulation. Cytokine. 2015;71:339-47.

c) Balkhi MY, Wittman G, Xiong F, **Junghans RP**. YY1 upregulates checkpoint receptors and downregulates Type I cytokines in exhausted, chronically stimulated human T cells. iScience 2018;2:105-122.

Research Support
Ongoing Research Support

NIAID/NIH 1R43/R44 (FastTrack) R44AI152709 (Junghans) 05/01/2020-04/30/2024
Advanced generation infection-proof anti-HIV CAR-T with YY1 RNAi to block T cell exhaustion in NHP model
This grant developed advanced generation infection-proof exhaustion resistant CAR-T cells for HIV therapy, tested in a non-human primate model in collaboration with the Tulane National Primate Research Center.
Role: PI Total costs: $4,100,000

NCI/NIH 1R43CA244048 (Junghans) 09/01/2019-08/31/2020
Co-targeting Ezh2 with PD1 to improve T cell exhaustion reversal and tumor responses
The major goals of this project are to test the synergistic benefit of co-applying checkpoint receptor therapy with Ezh2 inhibitors for antitumor responses in mouse models. Total costs: $250,000
Role: PI

DoD W81XWH-17-TSCRP-CTRA (LePoole) 09/01/2018 – 08/31/2020
Towards chimeric antigen receptor transgenic T cell therapy for Tuberous Sclerosis Complex
This grant aims to prepare for a clinical trial of anti-GD3 CAR-T therapy for TSC associated tumors
Role: Clinical CAR-T Consultant (anti-GD3 CAR, IND holder and clinical translation know-how provided to Dr LePoole by Dr Junghans) Total costs: $900,000

NIAID/NIH 4R33AI110158 (Braun) 09/01/2016- 08/31/2019*
Modifying CMV-Specific T Cells to Target HIV *on NCE
The major goal of this project is to explore how gene modified T-cell therapies can redirect the Immune System against HIV.
Role: Consortium PI Total costs: $600,000

Completed Research Support

1R56AI102847-01 (Junghans) 07/15/13 – 06/30/16
Towards a New Clinical Trial Advanced Infection Proof Anti HIV Gene Modified T Cells
This project focuses on developing a “functional cure” for HIV by exploiting a vulnerable step in the life cycle of HIV.
Role: PI

Department of Defense Grant # TS110036 (LePoole) 09/01/2012 – 08/31/2016
Developing Immunotherapeutic Options for Tuberous Sclerosis Complex (TSC)
This grant aims to elicit responses to TSC associated tumors in a pre-clinical model of TSC.
Role: Consortium PI

3R21AI110158 (Braun) 09/01/2014- 08/31/2016
Modifying CMV-Specific T Cells to Target HIV
The major goal of this project is to explore how gene modified T- Cell therapies can redirect the Immune System against HIV.
Role: Investigator