Agenda Item 1

Featured Start-Up – Living Pharma

UNIVERSITY SYSTEM of MARYLAND

BOARD OF REGENTS

SUMMARY OF ITEM FOR ACTION
INFORMATION OR DISCUSSION

TOPIC: Featured Start-Up Living Pharma, Inc. -- Introduction by Phil Robiloto; Presentation by Ron Dudek, Co-Founder and President (information item)

COMMITTEE: Economic Development and Technology Commercialization

DATE OF COMMITTEE MEETING: September 7, 2017

SUMMARY: The featured immunotherapy start-up, Living Pharma Inc., was one of the first investments of UMB's New Ventures Initiative and is the first to execute a successful exit. Living Pharma's technology provides the adaptability to target and destroy multiple cancer types, enabling the therapy to be tailored and optimized to the individual patient's cancer and disease phenotype.

The company was recently acquired by Lentigen Technology, Inc., a leader in the design, construction, and manufacture of lentiviral vectors. Lentigen Technology is located in Gaithersburg, MD.

Living Pharma's co-founder and Chief Scientific Officer, Dr. Eduardo Davila, is an associate professor of microbiology and immunology at the University of Maryland School of Medicine.

ALTERNATIVE(S): This item is for information purposes.

FISCAL IMPACT: This item is for information purposes.

CHANCELLOR'S RECOMMENDATION: This item is for information purposes.

COMMITTEE RECOMMENDATION: DATE:

BOARD ACTION: DATE:

SUBMITTED BY: Tom Sadowski (410) 576-5742 / Suresh Balakrishnan (301) 445-2783

Living Pharma, Inc.

Personalized CAR T-Cell Therapy™

Living Pharma History

- Incorporated December 17, 2015.
- Founders: Eduardo Davila, Ron Dudek, UMB.
- Davila,Tamada patent issuance January 12, 2016.
- Patent exclusively licensed by LPI January 28, 2016.
- LPI acquired by Lentigen Technology, Inc. June 29, 2017.

living PHARMA

Intellectual Property

- Living Pharma is the exclusive licensee of US 9,233,125
- Universal Anti-Tag Chimeric Antigen Receptor Expressing T Cells and Methods of Treating Cancer.

	US 9,233,125
Inventor:	Eduardo Davila, PhD, Koji Tamada, MD, PhD
Filed:	December 14, 2011
PCT Filed:	December 14, 2011
PCT No.:	PCT/US2011/064808
Issued US:	January 12, 2016
371(c)(1),(2),(4) Date:	June 12, 2013
PCT Pub. No.:	WO2012/082841
PCT Pub. Date:	June 21, 2012

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Davila, Tamada Publication

Published OnlineFirst October 2, 2012; DOI: 10.1158/1078-0432.CCR-12-1449

Clinical Cancer Research

Cancer Therapy: Preclinical

Redirecting Gene-Modified T Cells toward Various Cancer Types Using Tagged Antibodies

Koji Tamada[1,2,3], Degui Geng[1], Yukimi Sakoda[1,3], Navneeta Bansal[1], Ratika Srivastava[1], Zhaoyang Li[1], and Eduardo Davila[1,2]

Abstract

Purpose: To develop an adaptable gene-based vector that will confer immune cell specificity to various cancer types.

Experimental Design: Human and mouse T cells were genetically engineered to express a chimeric antigen receptor (CAR) that binds a fluorescein isothiocyanate (FITC) molecule, termed anti-FITC CAR T cells. Various antibodies (Ab) currently in clinical use including cetuximab (Ctx), trastuzumab (Her2), and rituximab (Rtx) were conjugated with FITC and tested for their ability to bind tumor cells, activate T cells, and induce antitumor effects *in vitro* and *in vivo*.

Results: Anti-FITC CAR T cells recognize various cancer types when bound with FITC-labeled Abs resulting in efficient target lysis, T-cell proliferation, and cytokine/chemokine production. The treatment of immunocompromised mice with human anti-FITC CAR T cells plus FITC-labeled cetuximab (FITC-Ctx) delayed the growth of colon cancer but unexpectedly led to the outgrowth of EGF receptor (EGFR)-negative tumor cells. On the other hand, in a human pancreatic cancer cell line with uniform EGFR expression, anti-FITC CAR T cells plus FITC-Ctx eradicated preestablished late-stage tumors. In immunocompetent mice, anti-FITC CAR T cells exhibited potent antitumor activity against syngeneic mouse breast cancer expressing Her2 and B-cell lymphoma expressing CD20 by combining with FITC-Her2 and FITC-Rtx, respectively. In addition, the activity of anti-FITC CAR T cells could be attenuated by subsequent injections of nonspecific FITC-IgG.

Conclusion: These studies highlight an applicability of anti-tag CAR technology to treat patients with different types of cancers and a possibility to regulate CAR T-cell functions with competing FITC molecules.
Clin Cancer Res; 18(23); 6436–45.

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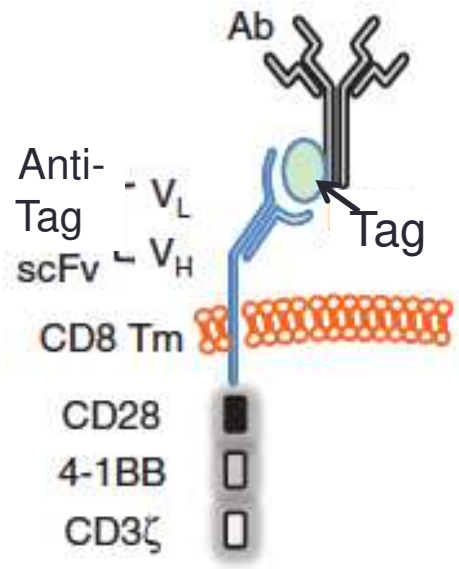
AT-CAR T™ Cell Product

- Anti-Tag Chimeric Antigen Receptor (AT-CAR)™ T cells are directed to tagged proteins.
- AT-CAR T cells seek out and kill tagged protein bound cancer cells.



AT-CAR Design:

- Anti-tag single chain antibody.
- CD28 and 4-1BB co-stimulatory domains.
- CD3 zeta activation domain.

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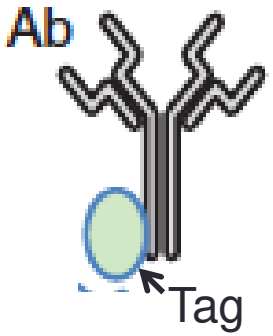
ATC™ Products

- Antibody Tag Conjugates (ATC's)™ are therapeutic antibodies that contain a tag recognized by the AT-CAR™ T cell.
- ATC's act as an on and off switch for the AT-CAR T cell and enable precise control of therapy.



ATC Design:

Antibody tagged with:

- Conjugated tags.
- Recombinant tags.

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Living Pharma Advantage

- Living Pharma's universal AT-CAR™ T cell can be directed to multiple targets.
- Direction comes from a panel of tagged therapeutic proteins which act as switches for the AT-CAR T cells.
- Control of both tagged protein dose and anti-tag CAR T cell dose promises improved control of therapy and improved control of treatment related toxicities.
- Single, sequential, and concurrent administration of tagged proteins delivers personalized CAR T cell therapy.
- Platform enables standardized CAR T cell manufacturing, e.g. CliniMACs Prodigy.
- And less complicated product development.
- FTO versus conventional CAR T cell IP.

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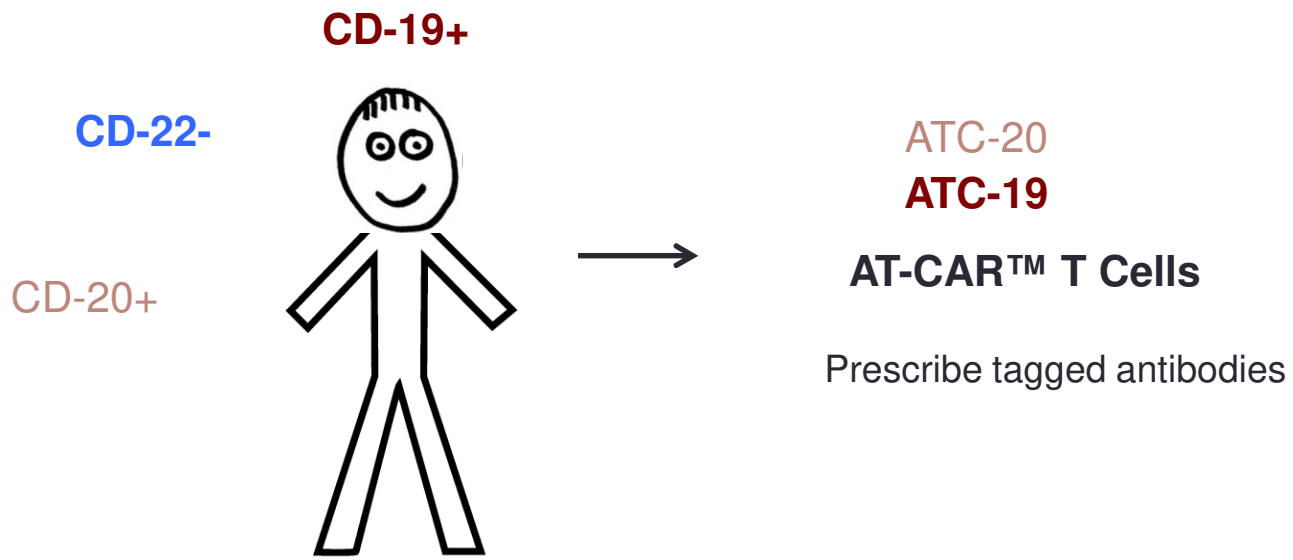
Personalized CAR T-Cell Therapy™

- A panel of Antibody Tag Conjugates (ATC's™) offers choices for personalized therapy.



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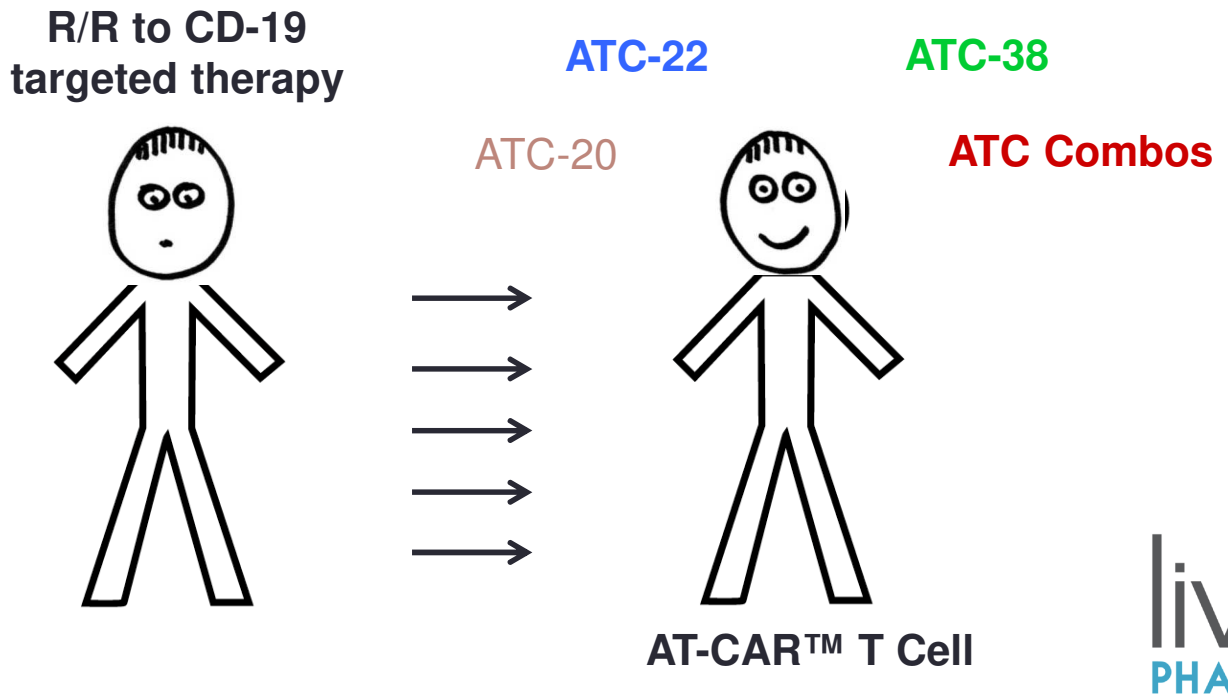
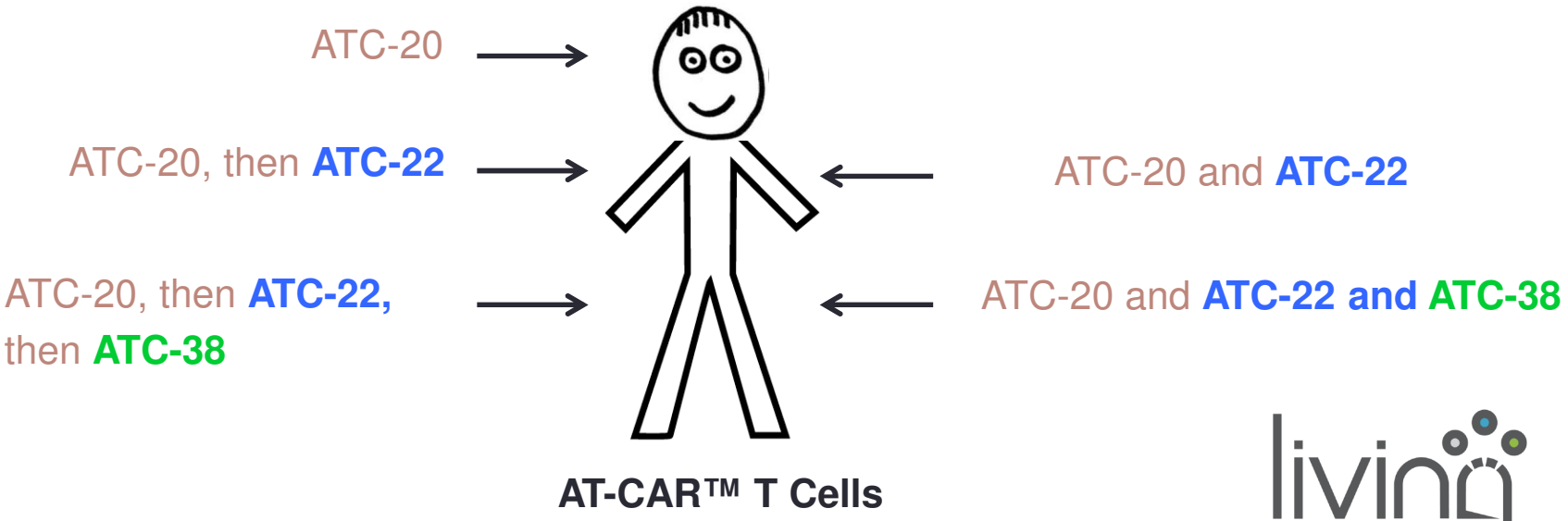
Personalized CAR T-Cell Therapy™

- A panel of ATC's™ offers multiple solutions for resistant and recurrent cancer.



Personalized CAR T-Cell Therapy™

- Sequential and concurrent administration now possible.



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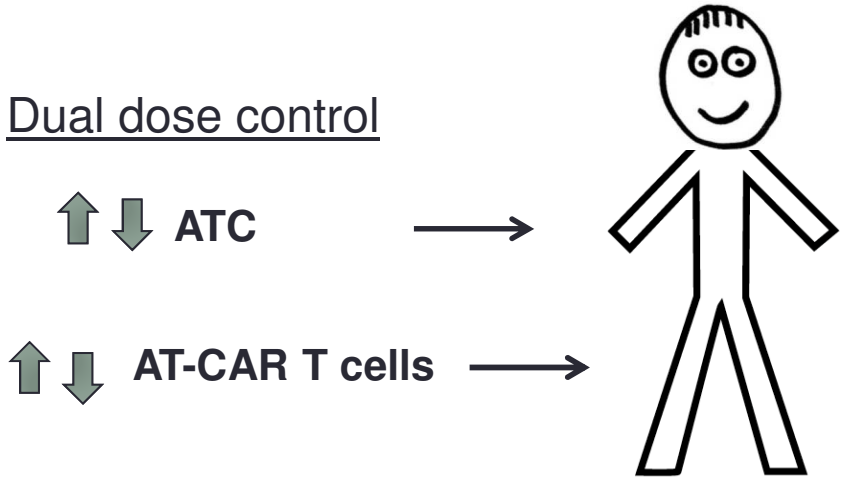
Personalized CAR T-Cell Therapy™

- ATC's™ act as a switch for the AT-CAR T cell.
- Withdrawal of ATC shuts off targeted killing without affecting CAR T cell.
- Control of both anti-tumor activity and cytokine secretion is possible.[1]



1. Switch-mediated activation and retargeting of CAR-T cells for B-cell malignancies. Proc Natl Acad Sci U S A. 2016 Jan 12. pii: 201524155

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Published AT-CAR™ Applications

CD19	Calibr	Pre-clinical	Leukemia. Lymphoma
CD20 rituximab	UMB Calibr	Pre-clinical Pre-clinical	Leukemia, lymphoma Leukemia, lymphoma
CD22	Calibr	Pre-clinical	Leukemia, lymphoma
CD33	GEMoaB/TU Dresden	Pre-clinical	AML
CD123	GEMoaB/TU Dresden	Pre-clinical	AML
BCMA	Unum Therapeutics	Pre-clinical	MM
Glypican-3	Unum Therapeutics	Pre-clinical	Hepatocellular carcinoma, NSCLC
HER2 trastuzumab	UMB Calibr	Pre-clinical Pre-clinical	Breast cancer, pancreatic cancer Breast cancer
EGFR cetuximab	UMB	Pre-clinical	Pancreatic, colon cancer
PSCA	GEMoaB/TU Dresden	Pre-clinical	Prostate cancer
PSMA	GEMoaB/TU Dresden	Pre-clinical	Prostate cancer

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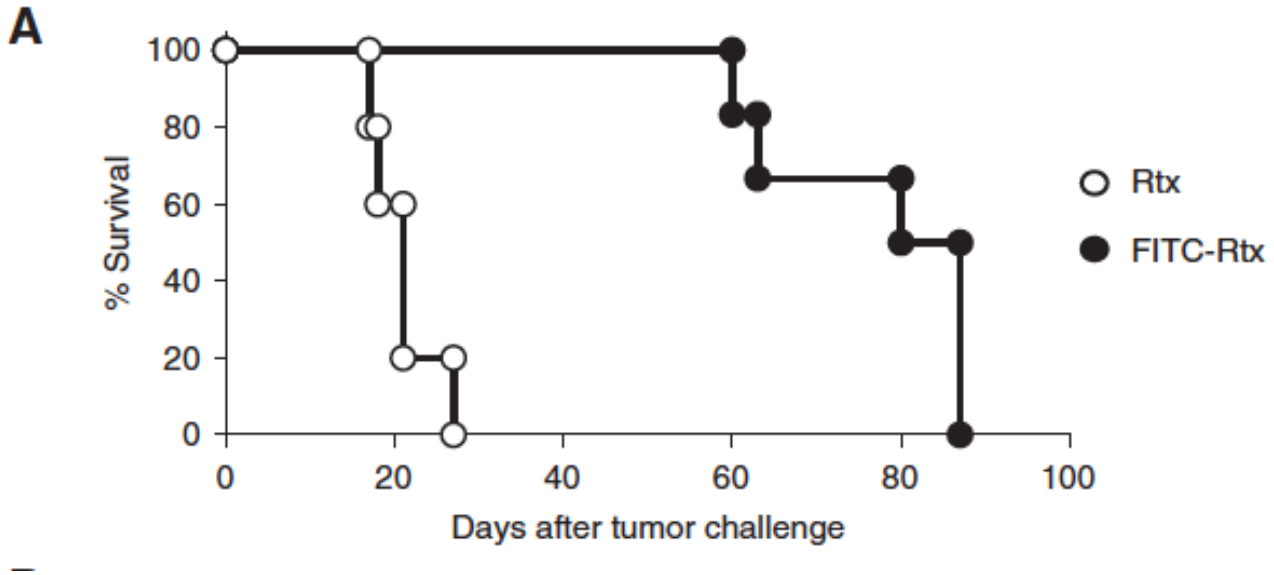
Preclinical *in vivo* Anti-Tumor Data

Rituxan® ATC™ + AT-CAR™ T cells eradicate CD20+ tumor cells. Improved efficacy of rituxan?



C3H/HeN mice were inoculated i.v. with human CD20–positive 38C13 tumor cells. After 4 days, the mice were treated i.p. with Rituxan ATC or non-labeled Rituxan repeatedly every week for 3 times. One day after the first Ab injection, the mice were injected i.v. with AT-CAR T cells generated from C3H/HeN spleen T cells.*(In vivo antitumor effects targeting EGFR, Her2, and CD20. Clinical Cancer Research 2012; Dec 1;18(23):6436-45.)*

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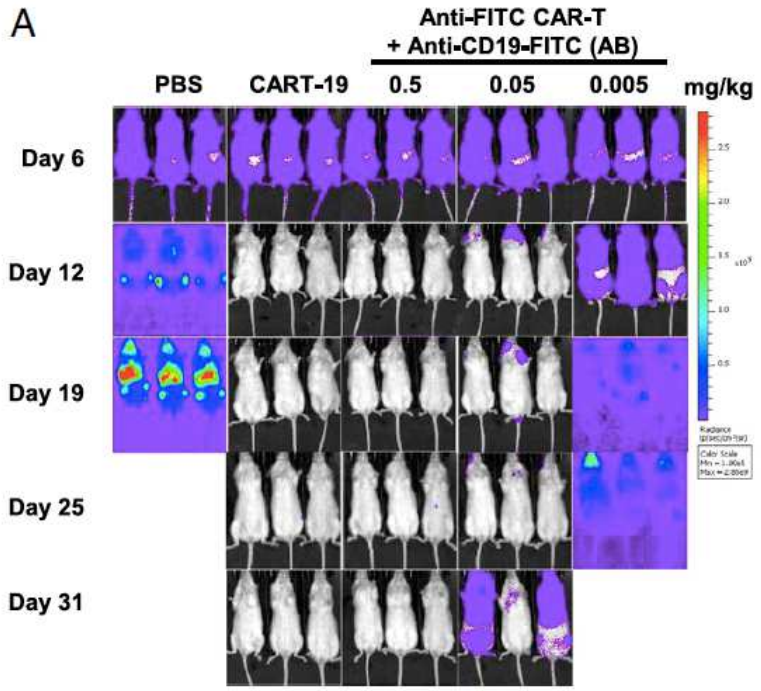
ATC™ Dose Titration

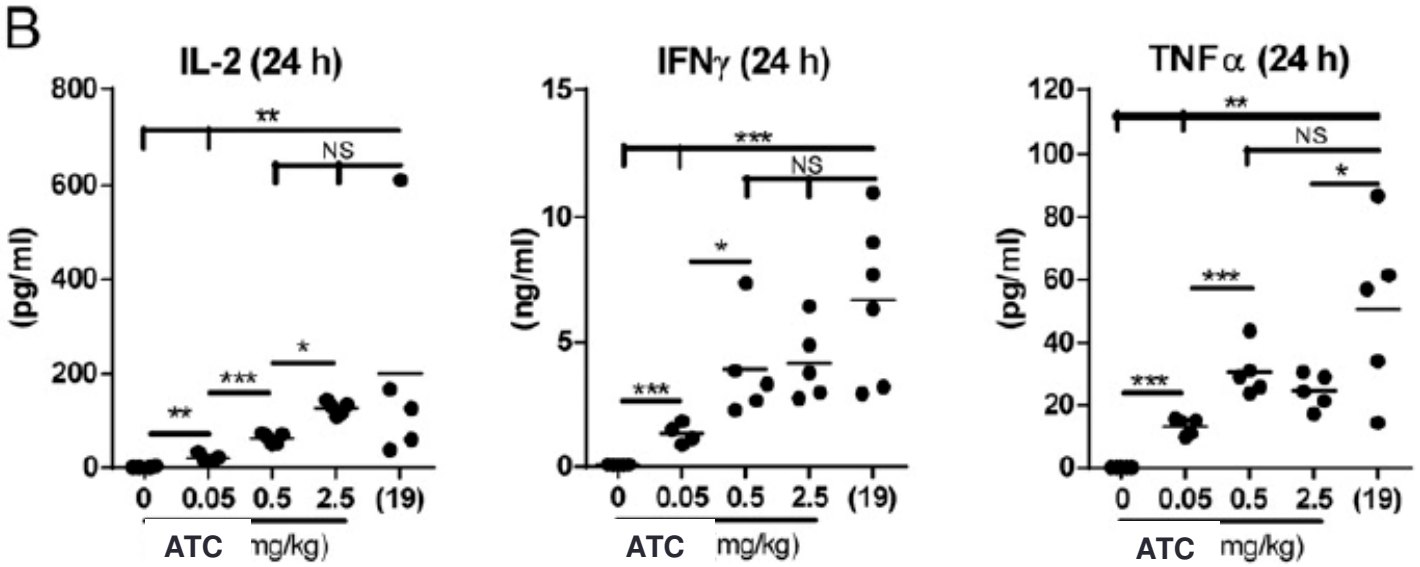
- CD19 ATC™ dose titration vs. conventional CAR T cell.



BLI of NSG mice inoculated with 0.5 x 10^6 Nalm-6 cells on day 0, and infused with 40x10^6 CART19 or AT-CAR T cells on day 6. On the day 7, anti-CD19 ATC was infused and at every other day for a total of six doses. *(Versatile strategy for controlling the specificity and activity of engineered T cells***.** Proc Natl Acad Sci U S A. 2016 Jan 12. pii: 201524193.)

ATC™ Dose Titration

- ATC™ dose titration allows separation of cytokine release from anti-tumor activity.



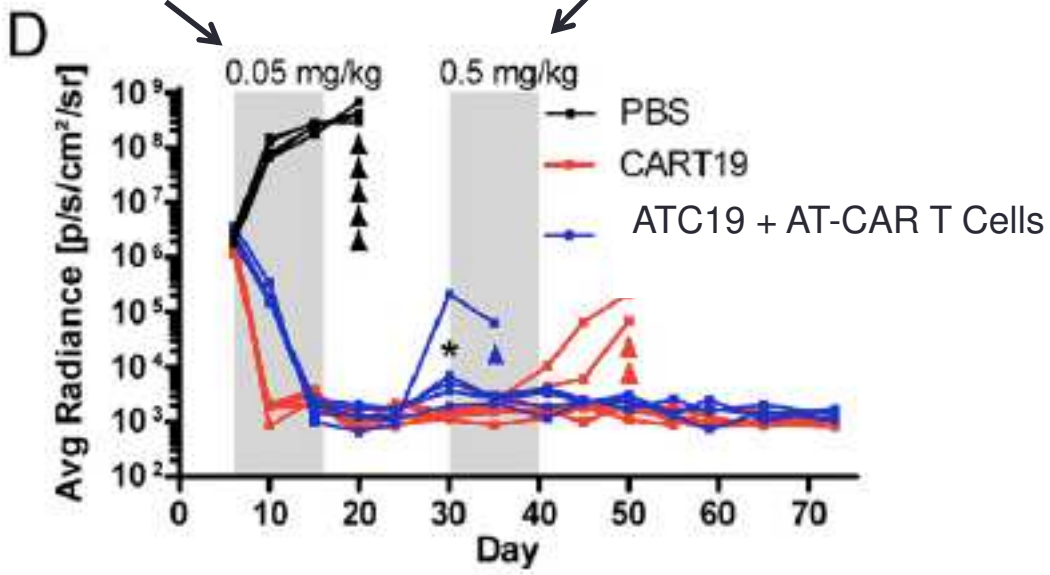
Levels of IL-2, IFNγ and TNFα after first anti-CD19 ATC dose, from groups dosed every day with 0, 0.05, 0.5 and 2.5 mg/mg of anti-CD19 ATC. NSG mice were inoculated with Nalm-6 and 6 d later were engrafted with AT-CAR-T cells. CART-19 is labeled as "(19)" (n = 5). *(Switch-mediated activation and retargeting of CAR-T cells for B-cell malignancies*. Proc Natl Acad Sci U S A. 2016 Jan 12. pii: 201524155.)

ATC™ Dose Titration

- ATC™ dose titration suggests clinical strategies.

Debulk with lower ATC dose.
Avoid CRS?

Eradicate tumor with higher ATC dose.
Avoid CRS?



Quantified tumor burden from mice dosed with 0.05 mg/kg CD19 ATC for 10 days indicated by grey shading (day 6-16). Dosing was resumed at 0.5 mg/kg when the average tumor burden in group became significantly higher that the CART-19 control at day 30, indicated by asterix and second grey shading (day 30-40). Triangles indicate the death of mice with significant tumor burden. *(Switch-mediated activation and retargeting of CAR-T cells for B-cell malignancies*. Proc Natl Acad Sci U S A. 2016 Jan 12. pii: 201524155.)

Potential ATC™ Panels

Disease	Targets					
B-Cell leukemia and lymphoma	CD19	CD20	CD22	CD30	CD37	Kappa, lambda light chain
Multiple myeloma	CD38	CS1	CD33	CD138	BCMA	CD74
AML	CD33	CD123	WT1	CD13	CD15	CD45
Solid organ cancer	Her2/neu	EGFR*	IG1-R	Mesothelin	CEACAM5	PSMA

*Anti-EGFR CAR T cell may not have a kras mutation limitation.

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Living Pharma Acquired

Lentigen Technology Inc., a Miltenyi Biotec Company, Acquires University of Maryland, Baltimore CAR-T Cell Start-Up, Living Pharma, Inc.

A startup that spun out of research at the **University of Maryland School of Medicine** was acquired 18 months after forming.

In a deal announced this week, Living Pharma was acquired by **Lentigen Technology Inc.**, a Gaithersburg-based subsidiary of **Miltenyi Biotec GmbH**. Terms were not disclosed.

Living Pharma's technology focuses on CAR T-cell therapy, an emerging form of treatment that uses re-engineered versions of a patient's immune cells to target cancer cells. The technology, invented by UMSOM faculty member **Eduardo Davila**, is designed to regulate the treatment, and allow the treatment to target multiple kinds of cancer cells.

Biotech startups often take years to grow to the point of an exit. Along with the promise of the technology, UMB Assistant Vice President for Tech Transfer **Phil Robilotto** said Living Pharma's acquisition was the result of a concerted effort by the university to provide resources.

The intellectual property was identified as ideal for a startup, and cofounder Ron Dudek joined the company to build the business. Along with the way, the team behind UM Ventures' New Ventures Initiative including **Mark Lafferty**, **Rana Quarishi** and **Darryl Carter** handled a lot of the "legwork" involved in building the company, said Robilotto.

"Their role really is to help move these companies along and do a lot of the day to day work that is so important," he said.

They're also looking to increase the number of startups that form out of the university's 150 invention disclosures a year.

With this deal, Dudek is relocating full-time to Maryland and joining Lentigen. The larger company more resources to help the technology advance, Robilotto said.

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Miltenyi Biotec Capabilities

- GMP Lentiviral Manufacturing: Lentigen Technology, Inc.[1]
- Automated, closed system CAR T cell manufacturing: CliniMACS Prodigy.[2]
- GMP antibody and antibody fragment manufacturing: Teterow, Germany facility.[3]
- GMP antibody conjugation: Bergisch Gladbach (HQ)[4] and Teterow, Germany facilities.
- Proprietary tag to be used with Adapter CAR platform: information to be provided under CDA.

1

2

4

3

Clinical Translation Goals

- 2-3 proof-of-concept investigator initiated clinical studies using known antibodies.
- Known antibodies are FDA approved antibodies or antibodies in clinical studies.
- Investigator obtains antibody and sends to Miltenyi Biotec for GMP biotinylation.
- Miltenyi Biotec ships biotinylated back to investigator site.
- Anti-biotin CAR T cell is made at investigator site using CliniMACS Prodigy, or, at Sunnyvale, CA GMP manufacturing facility, or at Bergisch Gladbach GMP manufacturing facility for EU studies.
- POC studies will establish first-in-man Adapter CAR clinical use.
- POC study data will be utilized by Miltenyi Biotec to fine tune future translation.

For additional information

Ron Dudek
Adapter CAR Program Director
Office: 1-301-527-4295
Cell: 1-425-647-7446
E-mail: Ron.Dudek@lentigen.com
Website: http://livingpharma.com/

L-R: Ron Dudek, Dr. Eduardo Davila, Dr. Phil Robilotto.