Remarks to the
ACDRS-NIH Workshop:

Cell-Based Immunotherapy: From Bench to Bedside and Beyond
U.S. HEALTH CHALLENGES IN THE 21st CENTURY

• **Life Expectancy**
  - Among the 36 OECD* nations, the U.S. ranks 28th in life expectancy; 33rd in infant mortality; 32nd in suicide rate
  - In 2015 and 2017, life expectancy decreased in the United States

• **Sexually Transmitted Diseases**
  - Highest numbers ever reported in U.S.
  - >2 million; 50% in adolescents and young adults; resurgence of congenital syphilis

• **Influenza and Infectious Diseases**
  - Enhanced risks from pandemic influenza, emerging infectious diseases, anti-microbial resistance

• **Rogue States and Organizations**
  - Intentional chemical, biological, radiological, and nuclear attack

*Organization for Economic Development and Cooperation*
U.S. DRUG OVERDOSE DEATHS
THE MOST CRITICAL PUBLIC HEALTH CHALLENGE OF OUR TIME

SOURCE: NCHS, National Vital Statics System, Mortality
## GLOBAL HEALTH CHALLENGES IN THE 21st CENTURY

### INFECTIOUS DISEASE
- **Malaria**: 216M cases and 445,000 deaths annually
- **Tuberculosis**: 25% of world population infected 1.7M deaths annually
- **HIV/AIDS**: 36.9M people infected 1.8M new cases in 2017
- **Neglected Tropical Diseases**: >140 diverse communicable diseases affecting the poorest 1B people on the planet (examples include Dengue, Hookworm, Schistosomiasis)

### NON COMMUNICABLE DISEASE
- **Cancer, Cardiovascular Disease, Diabetes, Chronic Lung Disease** caused 37% of deaths even in low income countries

### RISKS OF PANDEMICS:
- Influenza, SARS, MERS, Ebola, others

### 16,000+ children die every day of preventable diseases
U.S. HEALTH CHALLENGES IN THE 21st CENTURY

Highest global spending on health: $3.3 trillion (17.9% of GNP)

Health care spending is predicted to reach $5.7 trillion by 2026

MASS GENERAL’S INPATIENT ADJUSTED COSTS PER LIVE DISCHARGE

OPPORTUNITIES FOR PUBLIC HEALTH TRANSFORMATION

Assistant Secretary for Health

Senior Advisor for Opioid Policy

USPHS Commissioned Corps

World Health Organization
PRIORITY FOR PUBLIC HEALTH INNOVATION ENVIRONMENT

• Orthogonal technologies and paradigms for the current most costly medical issues (for example, hemodialysis, falls, sepsis, pain)

• Technologies and approaches that allow for more advanced care outside of hospital settings including in rural environments

• Socio-behavioral approaches and distributive technologies to transform the current “sick care system” into a “health promoting system”

• Leverage big data, social networks, and digital platforms for public health, including epidemiology, prediction, prevention, and treatment
PRIORITIES FOR PUBLIC HEALTH INNOVATION ENVIRONMENT

• End U.S. infectious disease epidemics *within our technical control*: HIV, HCV, HPV

• *Genetic cures, cell therapies, and immunotherapies*

• A new paradigm for understanding and treating *neurodegeneration*

• *Global health security*: a ubiquitous global capacity for early warning, detection, diagnosis, rapid mitigation, and assured effective response built on a primary care infrastructure

• The *Commissioned Corps* as an agent of change
WHY GENETIC CURES, CELL THERAPIES AND IMMUNOTHERAPIES?

- Potential for long-term survival with high-normal quality of life (cancer, ID, regeneration, other applications)
- Potential for minimal iatrogenic near- and long-term side effects
- Potential for high patient acceptance
- Harnesses “natural healing mechanisms”
  - “fixes” the underlying biological problems and limitations

*Paradigm shift in medicine with extraordinary potential for broad impact beyond current applications*
ARE WE AT ANOTHER INTERNET MOMENT?
POTENTIAL APPLICATIONS IN INFECTIOUS DISEASES

• CURRENT

3rd party, cryo-preserved, “off the shelf,” virus specific T cell therapy for life threatening viral infections in patients post HSCT (at production costs <$500 per dose)

• FUTURE?

Allogeneic or autologous T cell therapy for immunosuppressed or non-immunosuppressed hosts?

- Multi-drug Resistant TB; Influenza; WNV
- Ebola; Smallpox
- HIV
CHALLENGES FOR CELL-BASED THERAPY

• Limited tumor specific antigens that are candidates for cell therapy
• Overcoming barriers to allogeneic therapy
• Overcoming tumor resistance to T cell killing
  – Limitations of single antigen targeting
  – Upregulation of inhibitory molecules
• Limited, arduous cell production facilities
• Traditional study designs and regulatory processes
• CRS
  – Lack of predictive models
  – Need for more effective prevention and treatment strategies
• Time for development and costs of therapy
DEVELOPMENT OF CELL THERAPY AGAINST RENAL CELL CARCINOMA
TRANSLATIONAL RESEARCH BY RADM RICHARD CHILDS (NHLBI/NIH)

2000
Allogeneic HSCT regresses metastatic renal cell carcinoma  

2008
Post-transplant donor derived CD8+ T cells recognize a HERV-E antigen expressed in 90% of kidney cancer cells but not normal tissues.  
(Takahashi Y,….Childs R. J Clin Invest 2008)

2011
HERV-E expression restricted to clear cell kidney cancer due to VHL mutation  
(Cherkasova E, …Childs R. Oncogene 2011)

2016
Identification of HERV-E transcripts encoding the HERV-E envelope in ccRCC. Peptides derived from HERV-E Env are targeted by CD8+ T cells.  
(Cherkasova E,…..Childs R. Cancer Res 2016)

2016
HERV-E specific TCR is cloned into a retroviral vector  
T cells transduced with this vector acquire cytolytic activity against ccRCC  
 manuscript in preparation

2018
First in human NIH trial of adoptive infusion of HERV-E TCR transduced T cells in pts with metastatic kidney cancer initiated.
DEVELOPMENT OF CELL THERAPY AGAINST RENAL CELL CARCINOMA
TRANSLATIONAL RESEARCH BY RADM CHILDS (NHLBI/NIH)

RCC Patient #1

1998

2007

2018

20 years post-transplant
CREATING VALUE FOR PATIENTS AND THE NATION

• Improving outcomes that matter to patients
• Improving outcomes that matter to society
• Reducing the “all inclusive” costs of the interventions
MOORE’S LAW FOR CELL THERAPY?

Moore's Law is the observation made by Intel co-founder Gordon Moore that the number of transistors on a chip doubles every year while the costs are halved (1965)
MOORE’S LAW AND DNA SEQUENCING

- Parallel processing and automation
- Breakthrough technologies
  - Illumina: NGS
  - Single molecule real-time sequencing
- Informatics
- Massive market-pull
THE FLYING MACHINE AND CELL THERAPY

The New York Times

“The flying machine which will really fly might be evolved by the combined and continuous efforts of mathematicians and mechanicians in from one million to ten million years”

October 9, 1903

“We started assembly today”
Orville Wright’s Diary
October 9, 1903