Broadening the Application of Cellular Therapies

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Patients Treated on Cell Therapy Studies at CAGT

Type of T Cell	Number Enrolled
Allogeneic donor virus CTL	178
Autologous EBV or LMP CTL	164
T cell genetically modified with CAR in lymphoma (CD19, CD30, kappa)	30
T cells T cell genetically modified with CAR in solid tumors (GD2, Her2Neu)	42
Allodepleted T cells (genetically modified with iCasp9)	40
LMP CTL genetically modified with DN TGFB	6
Third party multivirus specific CTLs	51
TOTAL	511

"This is a boutique single center therapy"

Complex Biological Therapies (Advanced Therapy Medicinal Products)

- Gene transfer vectors
- Somatic cells
- Engineered tissues
- Must consider biology of:
  - Cells
  - Vector
  - Transgene
  - Immune response to the vector
  - Physiological responses to modified cell or product

Complex Biological Therapies

- Resource intensive to initiate and complete a multicenter Phase II study
- Ensure the optimal product is chosen for later phase studies.
- Multiple parameters that can be optimized
  - type of target cell
  - manufacturing processes
  - vector choice
- Develop and validate ancillary laboratory studies

Infrastructure for Cell and Gene Therapy Studies

- Regulatory Support
  - Multiple layers of review
  - All conducted under IND
  - Division of responsibilities sponsor and co-ordinating center
- Ancillary Reagents
  - Cell Production
  - Vector Production and Testing

Issues

- Central versus distributed cell production
  - Minimally manipulated versus cultured products
  - Studies of patient specific products versus allogeneic cell lines
  - Expertise
- Who would hold INDs?

CBT's do not fit the Pharmaceutical Model

Not pharmaceutical since:

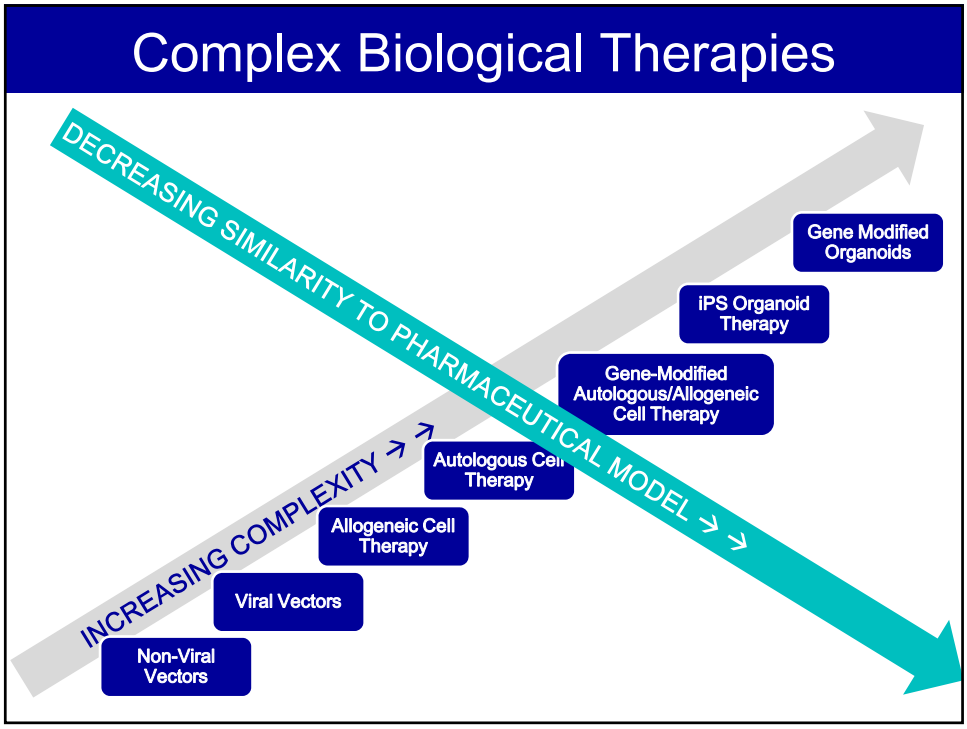
Often individualized

Complexity requires Iterative studies Lab-> Phase I->Lab->Phase I

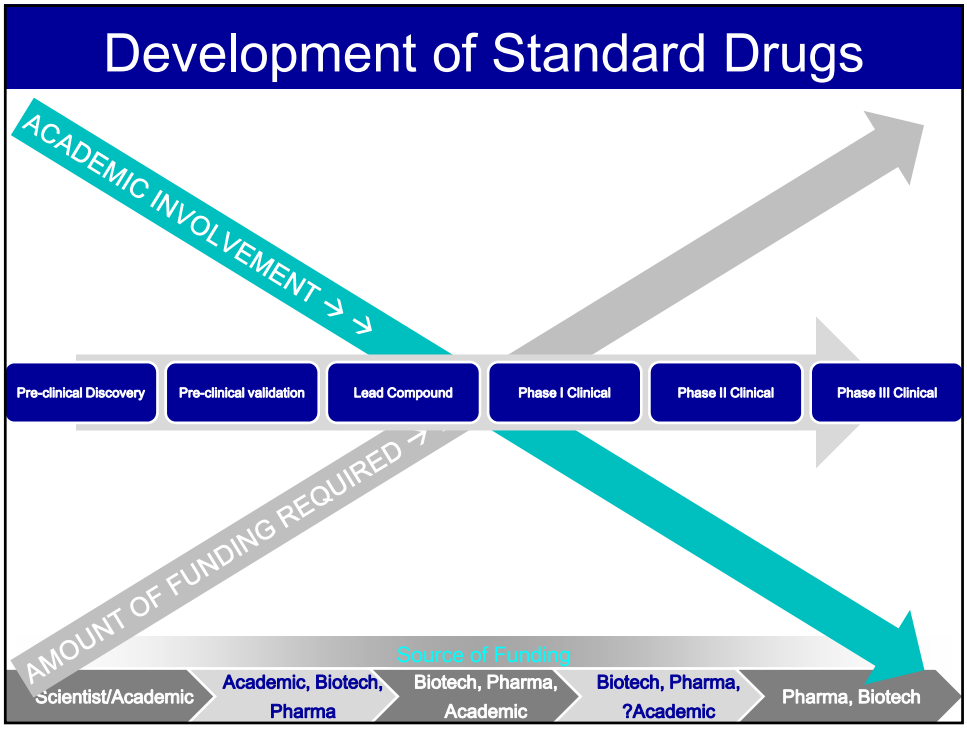
Complex extends to IP

High Cost of Goods

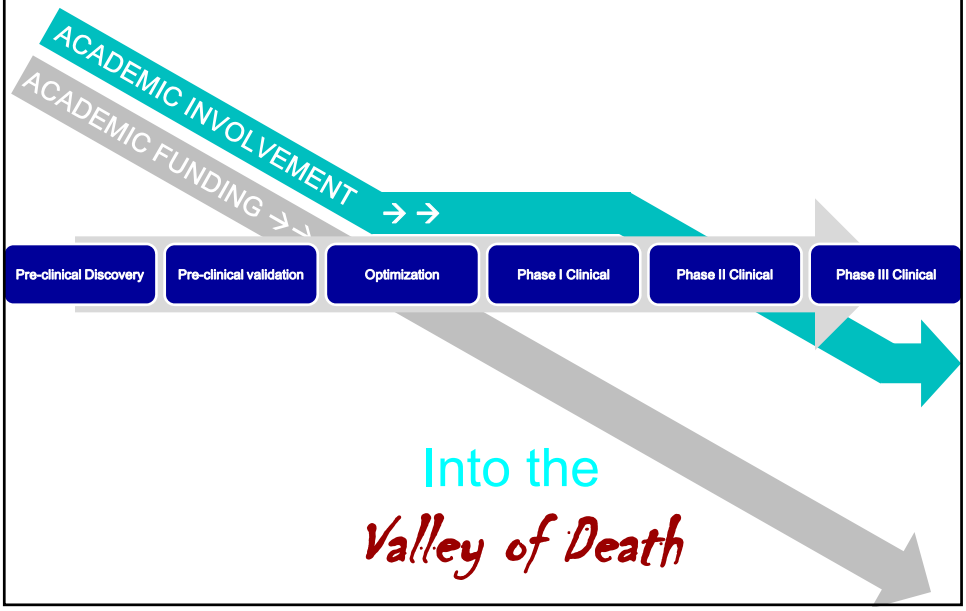
Complex Biological Therapies



Development of Standard Drugs



Development of CBTs



New CBT's No Longer Fit The Destination Model

Many pre-existing examples

- Hemopoietic Stem Cell transplant
- Solid Organ Transplant
- Invasive Cardiovascular Medicine
- High cost physical procedures (gamma-knife, proton beams etc)

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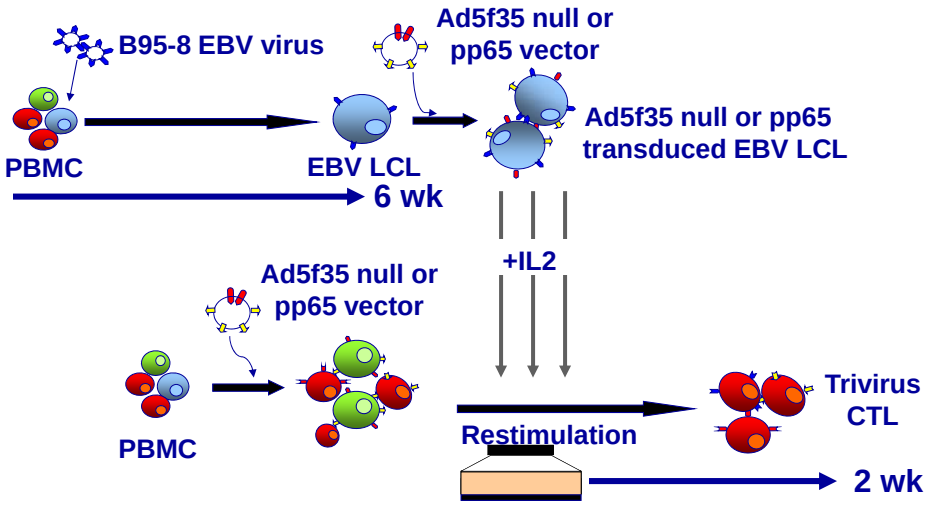
Regulatory and financial environment increasingly hostile to new, expensive "Practice of Medicine" therapies.

How to Make CBTs Worth the Effort

For wide implementation CBTs must be

BETTER	Phase I show clear efficacy
BROADER	One platform many diseases
SIMPLER	Cheaper and more transportable)
SAFER	Highly scrutinized (cf gene therapy

Generation Of Multivirus-specific CTL Using Ad5f35 Vectors



Sili et al Cytotherapy. 2012 Jan;14(1):7-11.

Multivirus Specific CTLs

- Expansion and persistence of CTLs specific for latent viruses EBV and CMV
- Adenovirus-specific CTL expand only in presence of adenovirus infection
  - Can reactivate adenovirus-specific response ex vivo by stimulation
- Responses to infections with all 3 viruses – overall response rate 93%

Leen et al Nat Med. 2006;12:1160-1166

How Do We Extend Applicability?

Limitations are

- –Cost
- –Complexity
- –Time

Manufacturing Costs Of Trivirus Specific CTL Production

Cost Item	
GMP facility	$2,280
Trained technician	$2,000
CTL line manufacture	$3,076
Release testing	$3,203
TOTAL	$10,559

Standard Treatment Charges
Rituximab for EBV-PTLD $9,000-$11,000
Ganciclovir for CMV $15,000

How Do We Extend Applicability?

Reduce Time to CTL Availability

- Use bank of allogeneic matched CTLs
- Simplify production patient specific product

Extending Applicability Banked Allogeneic Matched CTLs

- 50% response rate in Phase II study for PTLD post solid organ transplant

  Haque et al Blood 2007

- EBV CTLs induced CRs in 4/5 patients with PTLD

  Barker et al Blood 2010

  Doubrivina et al Blood 2011

Most Closely HLA Matched Allogeneic Virus Specific Cytotoxic T-Lymphocytes (CTL) to Treat Persistent Reactivation or Infection with Adenovirus, CMV and EBV after Hemopoietic Stem Cell Transplantation

CAGT
Helen Heslop
Ann Leen
Clio Rooney
Cath Bollard
Malcolm Brenner
Adrian Gee

Other Sites	
MDACC	EJ Shpall
Harvard	Joe Antin, B Dey
Duke	Paul Szabolcs
CHLA	Neena Kapoor
Children's Boston	Sun Yun Pai
Miami	Gary Kleiner
Hackensack	Scott Rowley

PACT
Production Assistance for Cellular Therapies

SCCT
Specialized Centers for Cell-Based Therapy
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Screening

- 81 patients screened
- Line identified for 72/81
  - Suitable line if matched at least one antigen with activity against infecting virus
- 9/81 no suitable line
- 24/81 with line not infused

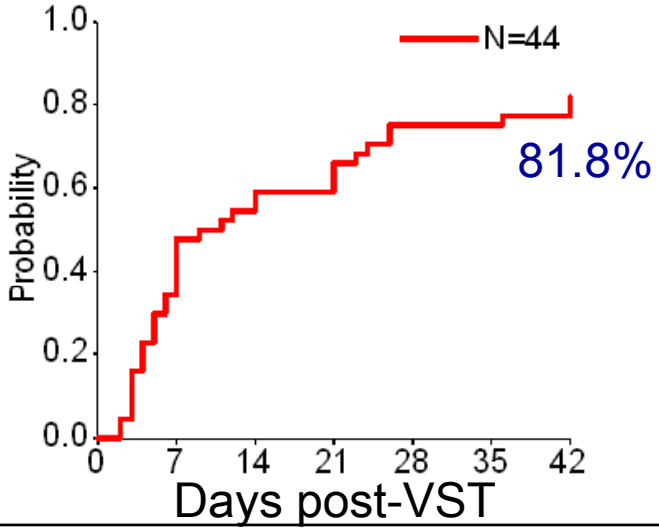
Patients Treated on Study

- 49 patients enrolled and infused
  - 5 subsequently excluded withdrawal/death within 7 days
- 44 evaluable patients
  - 19 received VSTs for CMV
  - 16 received VSTs for Adv
  - 9 received VSTs for EBV

Overall Response Rate

Cumulative incidence of CR/PR

- Based on viral load by day 42 post-infusion



Conclusions

- Low attributable toxicity
- VSTs effective in clearing EBV/Adv/CMV disease
- T cell expansion seen in around 50% of responders
- May require several infusions to sustain benefit
- Persistence for 12 weeks in a recipient of a 4/6 matched line

Allogeneic Trivirus T Cells

BETTER	Promising Phase I results
BROADER	Multiple viruses
SIMPLER	Used for many individuals but manufacturing complex
SAFER	Safe but still use viral vectors

Remaining Questions?

- How many lines do we need?
  - Edinburgh group estimated 22-26 to match 75% at least 3 loci
- Mechanism of action
- What is the best process for CTL manufacture?
  - Plasmids/peptides
- Monovirus versus multivirus
- Acceptable endpoints for FDA

What Are Requirements For Banked Cells?

- Donor evaluation
- Level of testing of banked lines
- Edinburgh group manufacturing new bank with optimal donors

Banked Viral-Specific T Cells

- Type C meeting with FDA
- More extensive master bank testing for late phase studies if still use viruses
- Simplified methodology plasmids or peptides (Ann Leen)
- Expanded access study old bank
- Make new bank with simpler methodology

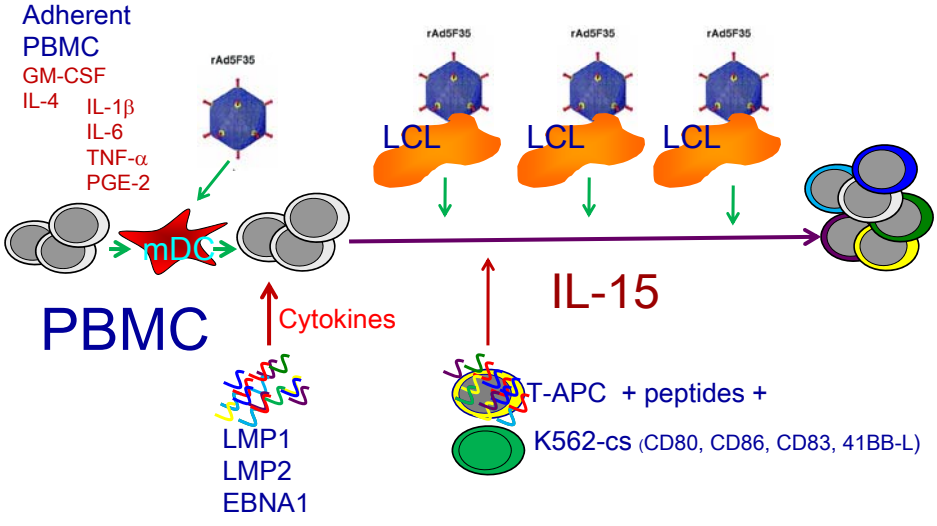
LMP Specific T Cells

BETTER	Promising Phase I results
BROADER	Apply to many EBV-associated malignancies
SIMPLER	Current manufacturing complex
SAFER	Safe but still use viral vectors

Moving to Phase II Studies – The Issues for LMP-CTL

- Agreeing on the "right" cells and how they should be manufactured
- Cell dose
- To lymphodeplete or not
- Study Design
- Target disease

Replace Ad-LMP1/2 with Pepmixes Replace LCLs with Auto-T-APC/K562-cs



Moving to Phase II Studies – LMP-CTL

- Licensed to Cell Medica
- Cell Medica secured funding from CPRIT for late Phase trial
- Focus on NK-T lymphoma

Economic Routes Favorable Pharmaco-economics

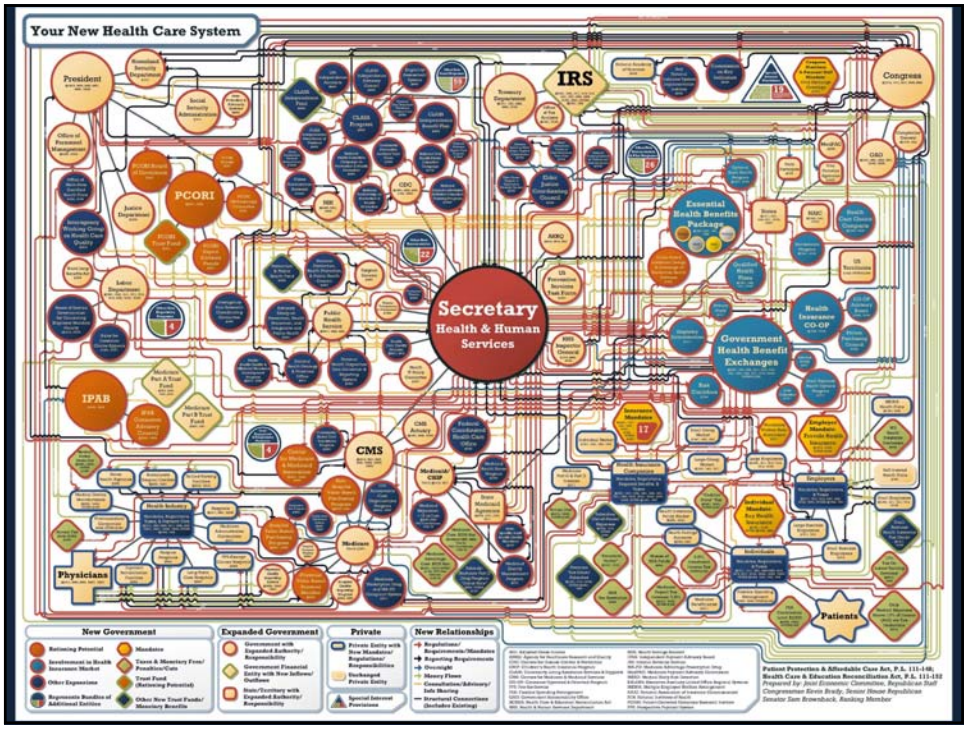
- Single payer favors pharmaco-economic arguments (“NICE”)
- Early phase cost/comparative effectiveness research essential

Economic Routes
"Pay-as-you-go"

- Cost recovery
- Include therapies within Case Rates
- Fast track Orphan Drug designation

Economic Routes
Novel Approaches

- Extend Provisional FDA Approvals with extensive post trial monitoring
- Annuity model "paying if still playing"
  - Easy for protein replacement therapies
  - Feasible for Cancer?



Conclusions

- Expanded T cells have clinical activity
- Broader applicability
  - Robust manufacturing processes
  - Clinical distribution paradigm
  - Cost effectiveness

Acknowledgements

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