CHARLES RIVER C&GT 360° SOLUTIONS

CAPABILITIES & GUIDANCE YOU CAN TRUST

EVERY STEP OF THE WAY

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EXECUTIVE SUMMARY

Integrated and Aligned End-to-End Vector and Cell Production: Charles River C&GT 360° Solutions

- Cell & Gene Therapy
  - Global Market and Trends
  - Charles River C&GT Mission and Strategic Focus
  - C&GT Development Pain Points
- Charles River C&GT 360° Solutions
  - Developing an Integrated End-to-End Solution for C&GT
  - Delving into the C&GT CDMO Offering at Charles River
  - Integrated and Aligned End-to-End C&GT program development

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C&GT MARKET AND TRENDS: CRL MISSION & STRATEGIC FOCUS

The C&GT market is growing and evolving quickly

C&GT market overall	C&GT market sub-segments	Emerging trends
$13-18B C&GT market (ex. China) by 2026	GM-Cell Therapy fastest growing C&GT segment (51% CAGR)	Emerging use of stem cells (blood, bone marrow), CD34+, IPSCs, and MSCs
1,174 C&GT companies 46% NA, 25% APAC, 18% EU	GM-Cell Therapy dominates oncology Gene therapy in rare disease & CNS	Increasing number of "gene-therapy-like" drug candidates (mRNA, RNAi, antisense oligos)
US #1, China #2, EU/UK #3 Korea & Japan growth >30%	Small & Mid-biotechs dominate Sci. & Reg. support needed from CRO/CMO	New & diverse business models are emerging Risk-shared builds New PD / mfg. platforms
C&GT pipeline 26% CAGR 1 out of 5 new candidates is C&GT	Autologous and allogeneic CTx growing at 30% GM-allogeneic growing faster than autologous	Internal CMC build by clients Intense regulatory scrutiny of CMC for product life

CRL is strongly positioned to support the development of advanced therapeutics

Our Purpose

We are dedicated to **accelerating** Cell and Gene Therapy research so, together, we can **create healthier lives**

Our Mission

To be the **most trusted**, **widely-used** Cell and Gene Therapy Services Platform and Ecosystem worldwide

Our Focus

Expand our portfolio of Cell & Gene Therapy capabilities to enhance our ability to **meet client needs** and provide the **fastest development** turnaround times

Charles River has the tools, talent, experience and capacity to support your CGT needs:

Conducted **>900** cell & gene therapy studies in 2020

Supported the development of **10** FDA-approved cell & gene therapies

100+ years of combined scientific experience

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Challenge: Complex & Fragmented C&GT Development Network

Numerous external relationships during development lifecycle complicate timelines & program management

Discovery & Design

In vivo

Clinical Trials

In vitro

Manufacturing & Testing

Delivery

Scientific & Regulatory Considerations

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Solution: Integrated C&GT Development Platform

Shared systems, faster knowledge transfers & process crossovers reduce bottlenecks & accelerate development

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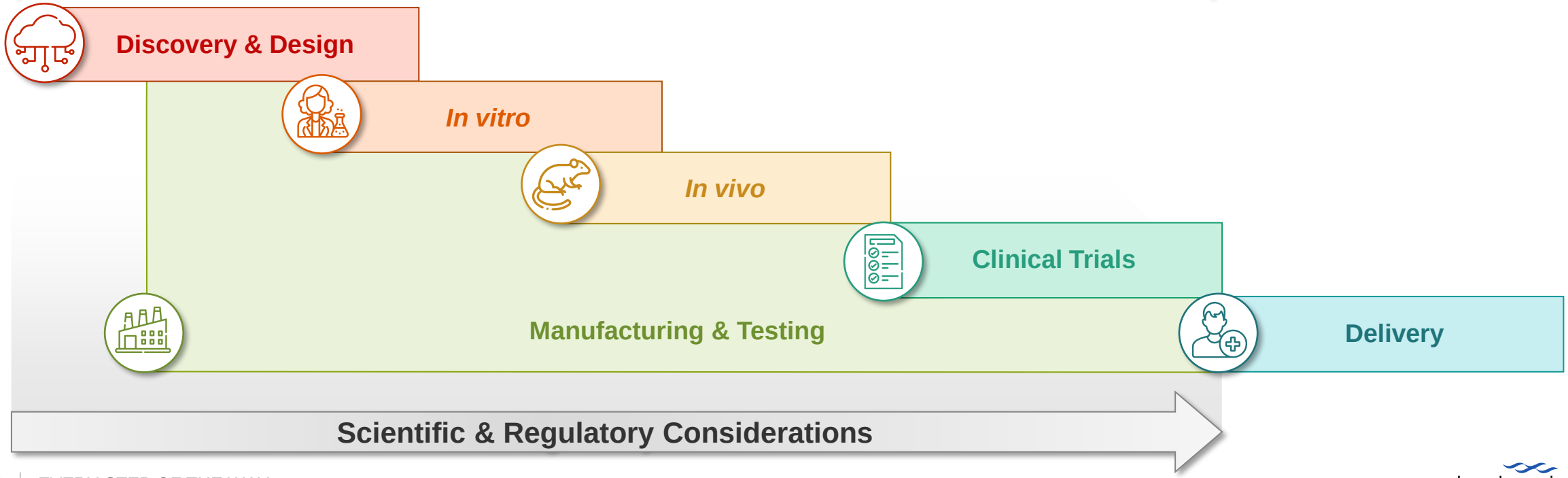
Accelerate and Achieve your C&GT Goals



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Charles River's C&GT 360° Solutions

Our integrated capabilities can support the entire development lifecycle

Enter at any stage along your C&GT development journey

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Charles River's C&GT 360° Solutions

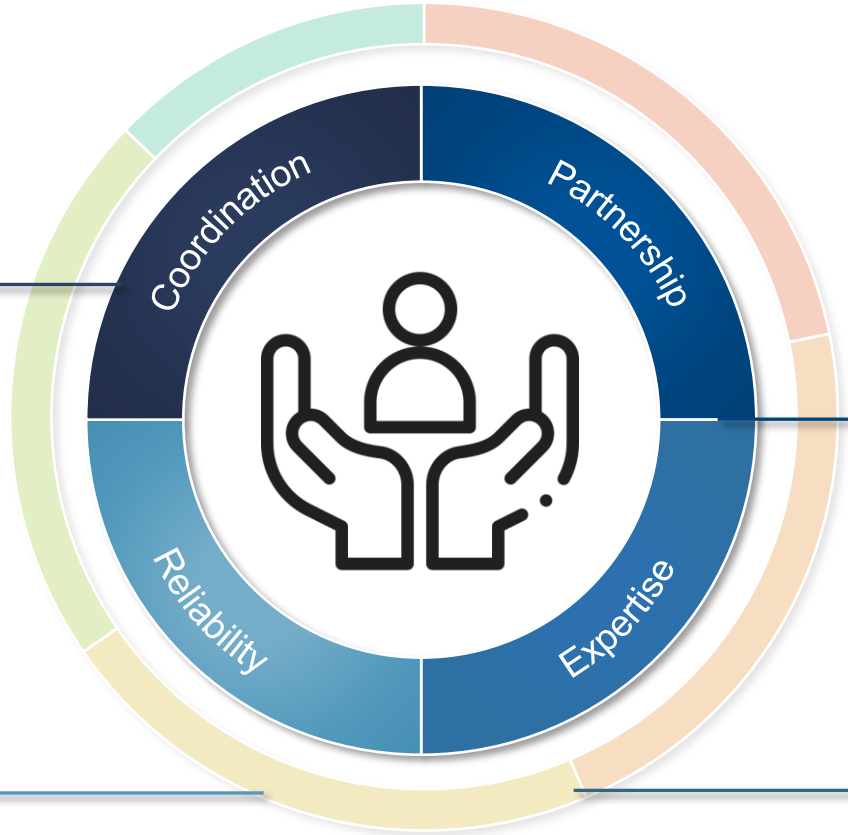
Our integrated service minimizes common pain points & frustrations when working with CROs & CDMOs

Alliance Manager

Accelerates program by planning and **coordinating logistics** as it moves through the CRL workflow

CGT Navigator

Understands the journey from concept to commercialization including CDMO/CMC. Acts as **strategic/technical consultant to map and drive program development through the CRL CGT portfolio.** Proactively coordinates with site/BU-specific PMO to move process between sites in the CGT portfolio while collaborating with SAS and ALM.



COMING SOON!

Digitized Customer Portal

Make decisions quickly and readily view **results; track program status** to help with planning and avoid program delays

Scientific & Regulatory Advisors (SAS)

Provide in-depth expertise to enable your journey for each **critical milestone**

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CHARLES RIVER C&GT 360° SOLUTIONS

Our integrated C&GT CDMO capabilities can support the entire development lifecycle

Cell and Gene Therapy Products

We are the leading provider of high-quality clinical-grade, GMP-compliant human cellular material, plasmid and viral vectors

Biologics Testing

Tailored global biologics and large-molecule testing and manufacturing services to support clients anywhere in the world throughout the biologics development cycle

Development and Manufacturing

CDMO services to rapidly develop products from bench to bedside and ultimately to commercial including GMP cell therapy manufacturing, Plasmid DNA production (RUO thru CGMP), and viral vector production (RUO thru GMP).

CHARLES RIVER DEVELOPMENT & MANUFACTURING C&GT 360° SOLUTIONS

Multiple acquisitions strengthen our ability to service client needs

COGNATE BIOSERVICES A Charles River Company

Baltimore, MD
Memphis, TN

Focused expertise in cell

COBRA BIOLOGICS A Charles River Company

Keele, UK

Focused expertise in Lenti , Adeno & plasmid DNA

Vigene Biosciences A Charles River Company

Rockville, MD

Focused expertise in AAV, Adeno & plasmid DNA

Development and Manufacturing

CDMO services to rapidly develop products from bench to bedside and ultimately to commercial including GMP cell therapy manufacturing, Plasmid DNA production (RUO thru CGMP), and viral vector production (RUO thru GMP).

Cell and Gene Therapy Products

We are the leading provider of high-quality clinical-grade, GMP-compliant human cellular material, plasmid and viral vectors

HemaCare A Charles River Company

Memphis, TN
Northridge, CA
Bothell, WA
Lowell, MA

Research and GMP Compliant Human Cells

Donor recruitment & management

Cell collection, processing & isolation services

Storage, shipping & logistics

Vigene Biosciences A Charles River Company

Rockville, MD

Research to GMP-Ready Vectors and Plasmids

GMP-Ready Plasmids off-the-shelf

AAV Reference Materials

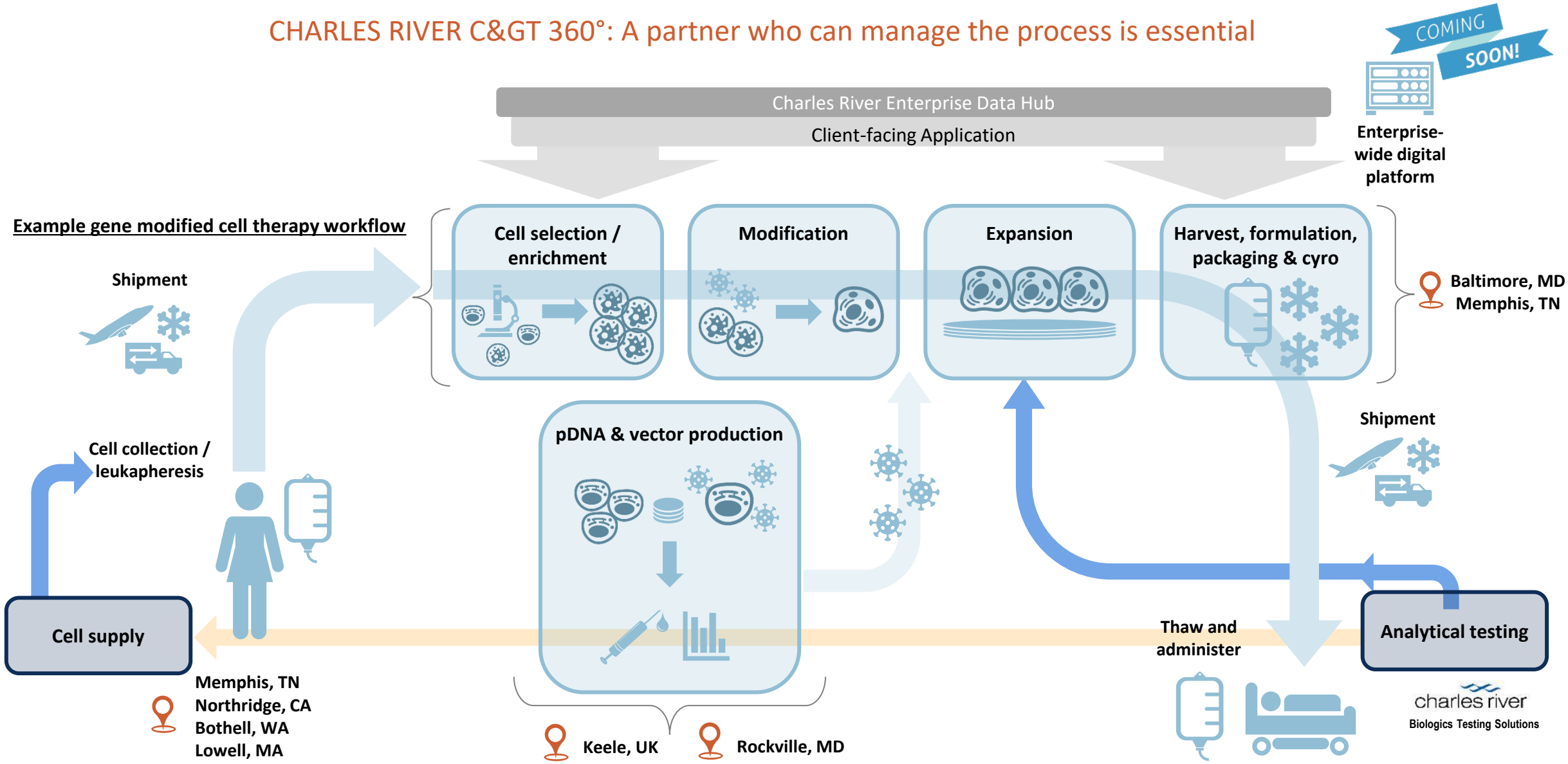
AAV Products

Lentivirus Products

Plasmid Product

WE CAN SERVICE THE ENTIRE CELL & GENE SUPPLY CHAIN

CHARLES RIVER C&GT 360°: A partner who can manage the process is essential



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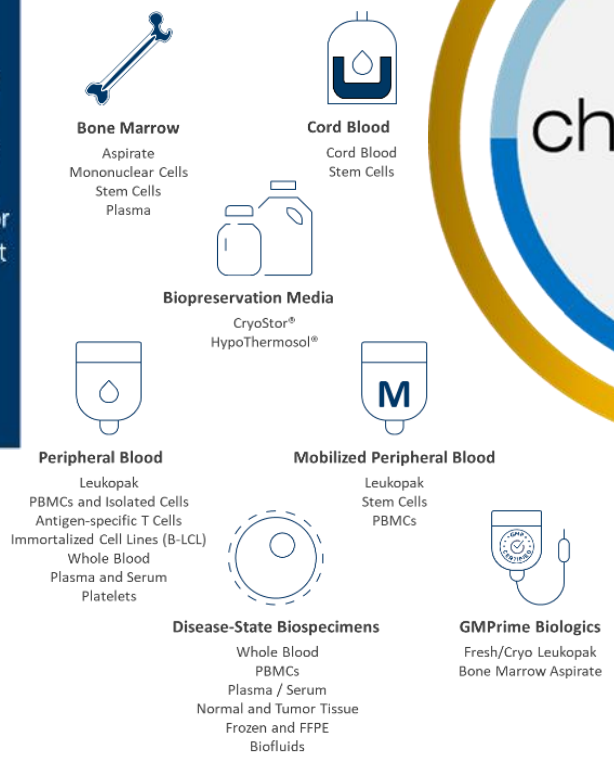
CHARLES RIVER C&GT 360° SOLUTIONS

We are a leading supplier of human cellular material

HemaCare
A Charles River Company

Supplied
200+
GMP-compliant products to support clinical-phase manufacturing for the development of allogeneic therapies



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C&GT 360°

Cellular Products

We are the leading provider of high-quality clinical-grade, GMP-compliant human cellular material.

Research and GMP Compliant Human Cells

40+
years of experience

300,000+
apheresis collections

Supplying GMP-compliant cellular material to
20+
allogeneic customers

Involved in
100%
of FDA-approved immune cell therapies

Credit: Terumo BCT

Donor recruitment & management

Cell collection & processing services

Storage, shipping & logistics

Memphis, TN
Northridge, CA
Bothell, WA
Lowell, MA

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CHARLES RIVER C&GT 360° SOLUTIONS

An integrated and experienced CDMO network strengthen our ability to service client needs

COGNATE BIOSERVICES
A Charles River Company

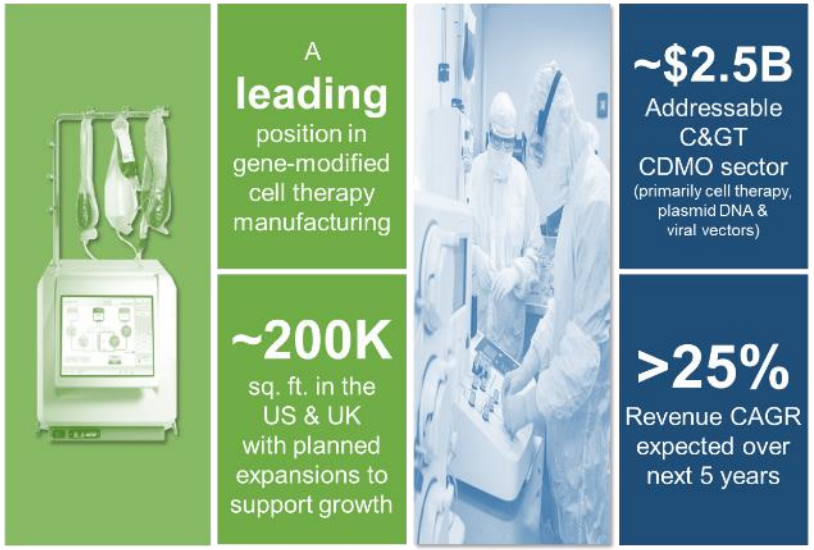
Focused expertise in Cell Therapies

COBRA BIOLOGICS
A Charles River Company

Focused expertise in LVV , AdV & plasmid DNA

Vigene Biosciences
A Charles River Company

Focused expertise in AAV, AdV & plasmid DNA



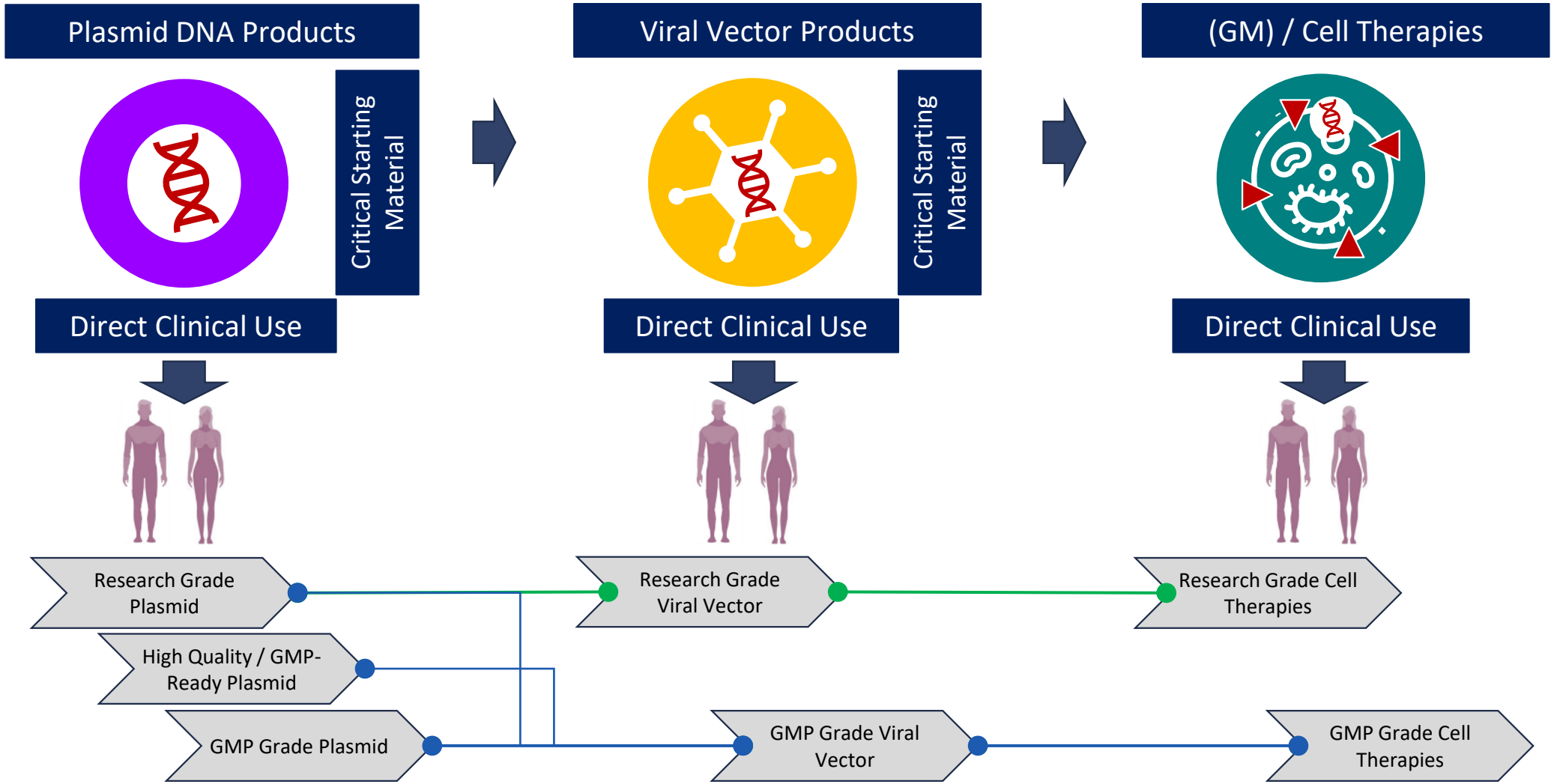
Development and Manufacturing

We provide manufacturing services for clients seeking rapid development of products from clinical studies into commercial scale manufacturing. This includes RUO and CGMP cell therapy manufacturing, plasmid DNA production, viral vector production and fill finish.

Synergistic fit with **Biologics Testing** to establish a premier partner for testing and manufacturing for advanced drug modalities

COMPLEX INTERDEPENENDENCY BETWEEN C&GT PRODUCTS

Multiple product types, and complex manufacturing supply chains are required to generate cell and gene therapies



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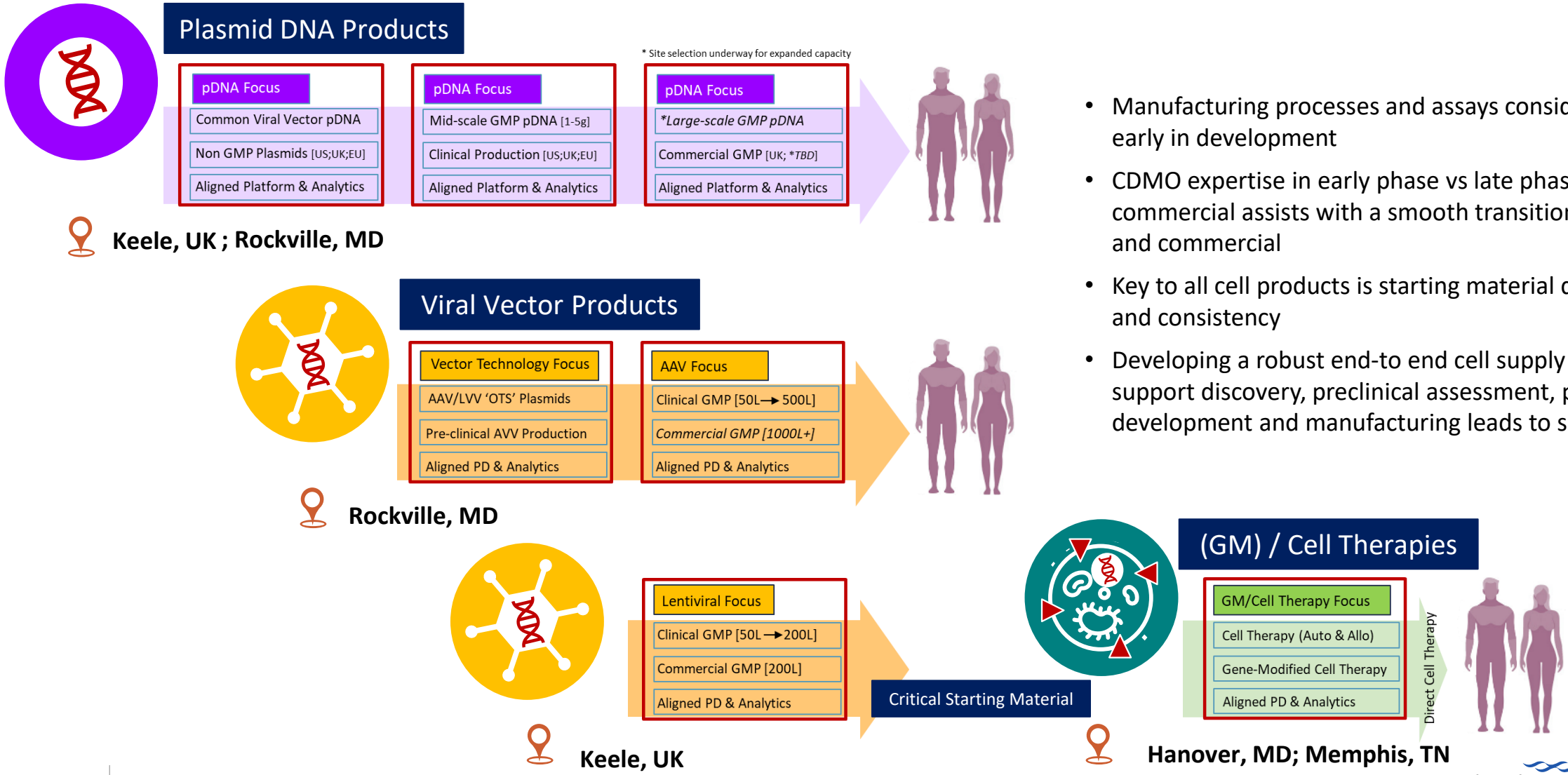
COMPLEX INTERDEPENENDENCY BETWEEN C&GT PRODUCTS

CRL's CDMO network can support the multiple product types required to generate a cell and gene therapy



- Manufacturing processes and assays considered early in development
- CDMO expertise in early phase vs late phase and commercial assists with a smooth transition to GMP and commercial
- Key to all cell products is starting material quality and consistency
- Developing a robust end-to end cell supply chain to support discovery, preclinical assessment, process development and manufacturing leads to success

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CRL'S CDMO NETWORK FOR C&GT PRODUCTS

Experienced CDMO's & properly positioned facilities facilitates smooth transition to GMP and commercial

Gene Therapy (UK/US)

Keele, UK

Plasmid DNA & Viral Vectors

- **Current Capabilities:**
  - 20-year track record in gene therapy
  - High-Quality Plasmid DNA & 50L GMP Plasmid DNA
  - Viral Vector Process Development & GMP Production
  - AD and GMP QC
  - MHRA IMPD / restricted MIA license
- **Future Expansion:**
  - Commercial DNA & viral vector supply
  - Expanded High-Quality Plasmid DNA

Rockville, MD

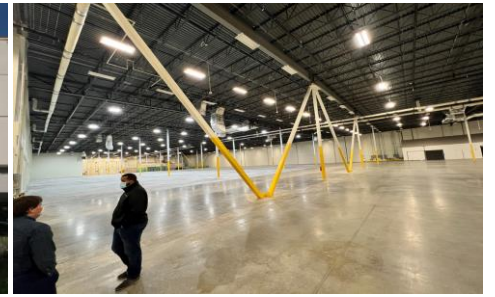
Viral Vector & Plasmid DNA

- **Current capacity**:
  - ~110K sq. ft. facility
  - 15 GMP cleanroom suites
- **Current Capabilities:**
  - 10-year track record in gene therapy
  - Viral vectors being used for gene delivery (AAV, AdV, LV, and retrovirus)
  - High-Quality and GMP Plasmid DNA
  - Viral Vector PD & GMP Production

Cell Therapy (US)

Hanover, MD; Memphis, TN

- CGMP cell therapy manufacturing
- **Current capacity**:
  - >10 years of GMP cell therapy production in Memphis
  - GMP cell therapy operations in 22 suites for US/EU standards
- **Future expansion**:
  - 9 additional suites by end of 2022
- **Other capabilities:**
- Process development, analytical testing, and logistics/supply chain capabilities
- Commercial-ready cell and gene therapy production capacity available



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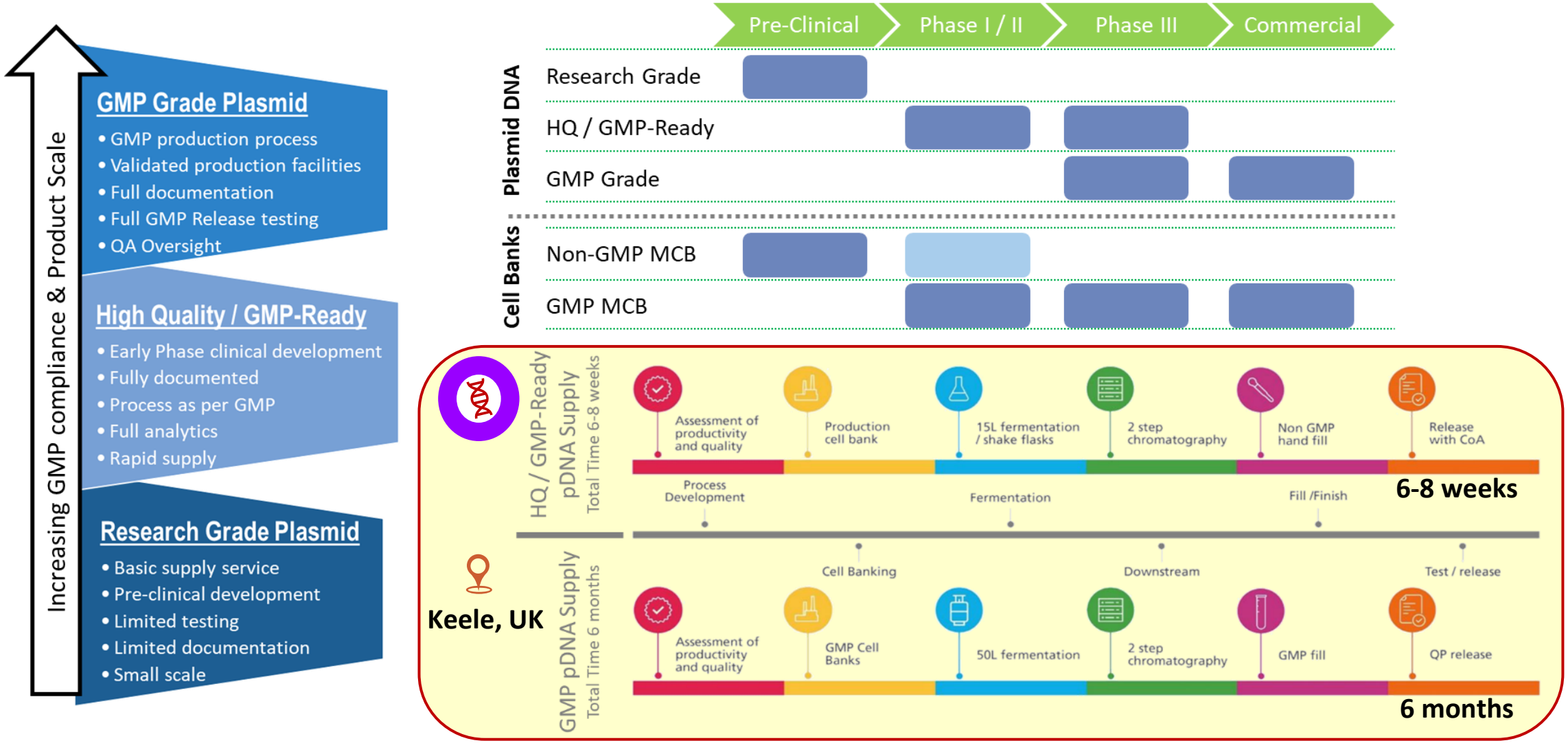
SOURCING PLASMID DNA FOR CELL & GENE THERAPIES

Phase & scale dependent approaches to pDNA production



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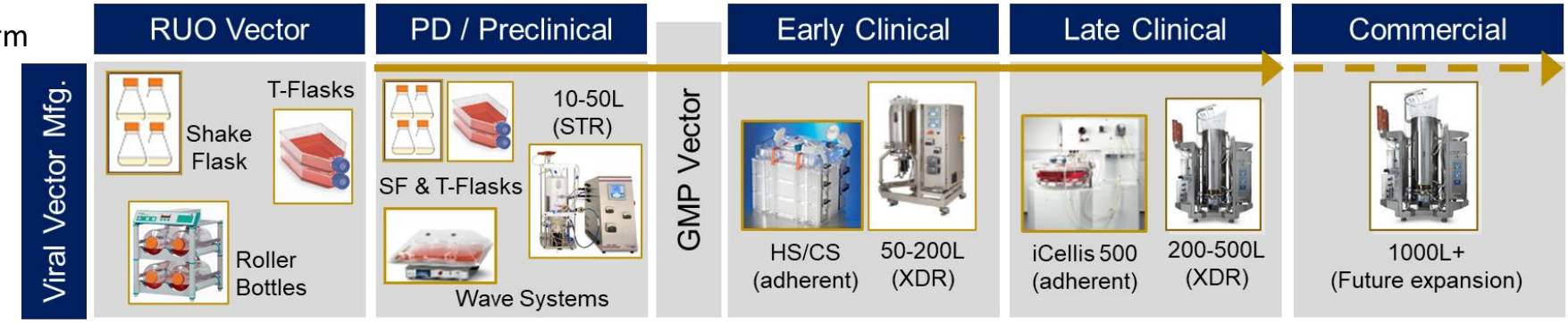
VIRAL VECTORS FOR GENE THERAPY & GENE-MODIFIED CELL THERAPIES

Centers of Excellence for all your viral vector needs for C&GT

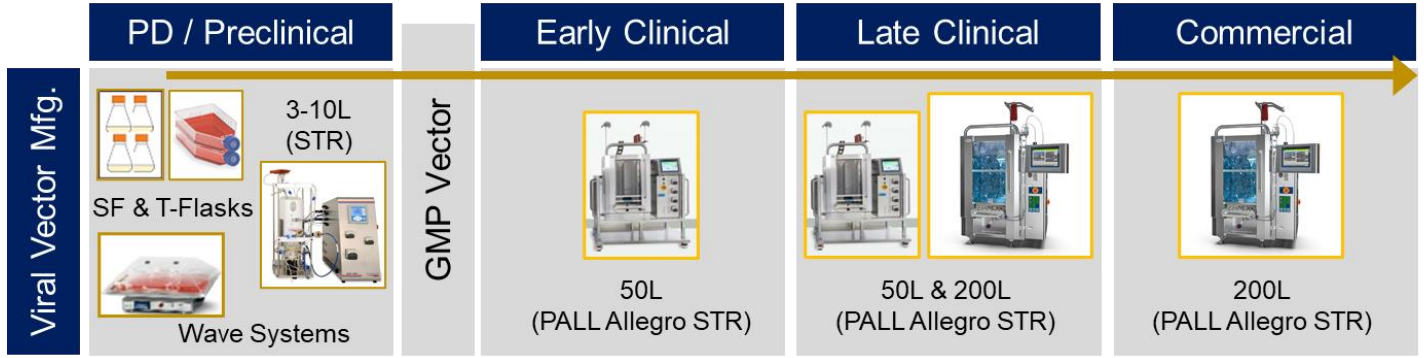
Rockville, MD: Primary focus area is AAV viral vector manufacturing

- Scalable production platform
- Adherent & suspension
- Off-the-shelf vector pDNA
- Aligned analytical testing



Keele, UK: Primary focus area is LVV & AdV viral vector manufacturing

- Scalable GMP production platform from PD to 200L GMP commercial-ready scale
- Suspension-based production approach in GMP
- Aligned with analytical testing platform
- MHRA IMPD & restricted MIA License



Our 20+ years expertise in viral vector development and GMP manufacture assists clients with a smooth transition from early phase, through late phase to commercial production.

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CELL THERAPY DEVELOPMENT & GMP MANUFACTURING

Fully integrated and experienced cell therapy CDMO

Extensive capabilities for scientifically complex, cell therapy development and manufacturing solutions

- Numerous cell therapy modality experience
- Specialists in process & analytical development

- Center of Excellence for process and analytical development
- MSAT, ClinOps, QA/QC/RA expertise in various jurisdictions

- Expertise in both autologous and allogeneic cell therapies
- Additional know-how generating GMP cell banks (MCB/WCB)

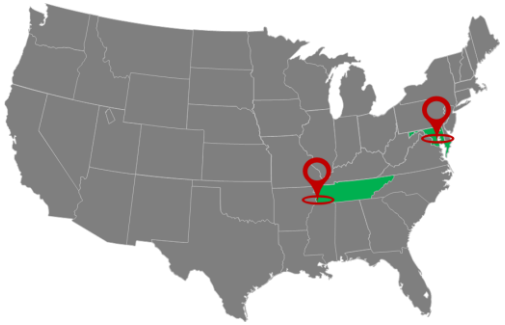
CGMP CELL THERAPY MANUFACTURING:

- MILs
- Dendritic Cells (DC's)
- Natural Killer (NK) Cells
- T-Cells
- Car-T
- BMSC's
- MSC's
- Whole Blood
- Apheresis
- Leukapheresis
- Tumor Isolate
- Stem cells (variety)

Cell therapies are personalized medicines produced in small batches/scales with customization

- Highly flexible blank slate production suites that are agnostic to equipment manufacturers

- Process scale from shake flask (<1L each) to 200L bioreactor systems
- Aligned with QA/QC for critical analytics and review
- Continuous improvement manufacturing
- From clinical phases to commercial-ready production



- Strategic position in NA's largest shipping hub to handle time-sensitive therapeutics & large trials

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CHARLES RIVER C&GT 360° SOLUTIONS

Integrated cell and gene therapy testing solutions

Biologics & Microbial Testing

We provide tailored global biologics and large-molecule testing and manufacturing services to support clients anywhere in the world throughout the biologics development cycle

We also deliver accurate, relevant, and reliable data to make confident decisions on product quality and contamination control

- **Safety testing, identify (vector/cells), purity/potency**
- **Objective sterility release testing**
- **Quantitative endotoxin testing**
- **Same day microorganism identifications**

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With 50 years of experience, CRL's comprehensive in-house testing portfolio supports over 200 licensed products for biotechnology and pharmaceutical companies worldwide

BIOLOGICS TESTING SOLUTIONS

Providing CGMP compliant testing solutions to ensure the safety, efficacy and potency of your product

Product and Genetic Characterization Services	Biosafety and Clearance Testing	Bio-Activity and Potency Testing	Manufacturing
•Biophysical Testing •Analytical Testing •Genetic Testing	•Viral Analysis •Microbial Analysis •HCP Analysis •Residuals Testing •Clearance Studies	•*In Vivo* Bioassays •*In Vitro* Bioassays •Analytical Testing	•Cell Bank Manufacturing and storage •Viral Bank Manufacturing and storage

- Cell bank, virus bank, and **raw material** biosafety testing
  - •PCR
  - •Microbiology
  - •Adventitious agent
  - •Replication competent virus
  - •NGS
- Cell bank, virus bank, and **product** characterization and release testing
  - •Identification
  - •Genome and infectious titer
  - •Residual host cell and protein
  - •Empty vs full virus particles
  - •Gene expression and potency
- Process validation/viral clearance studies for gene therapy product
- Stability testing

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RightSource: YOUR LAB IN A BOX

Insourcing solutions: Biologics testing support from CRL at your own cell/ gene/other manufacturing facility

RightSource is…

- End-to-end biologics testing *service provider*
- *L*ocated at your facility
- Fastest way to get setup for GMP testing (up to 40% reduction in timeline)

RightSource is *not*…

- Temporary staffing agency
- Outsourced services firm

Provided by client*

- All equipment
- Materials, reagents, consumables
- Strategic direction of all R&D
- Fully built-out lab

**With CRL Input*

Provided by CRL

- CRL Employees
- Scientific Expertise
- Day-to-day Management of testing lab
- Assays, Methods, SOPs (as needed)
- Quality Systems (as needed)
- Priority scheduling for samples sent to a CRL site

Microbiology Services | **Process Development Testing and Support** | **Analytical GMP Release Testing**

MICROBIAL SOLUTIONS FOR CELL AND GENE THERAPIES

Endosafe® Endotoxin Testing Instrumentation	Celsis® Sterility for Cell Based Samples	Celsis® for ATMP, Short Shelf Life	Accugenix® Microbial Identification & Strain Typing
			
• Rapid, convenient, real-time endotoxin testing • 15-minute quantitative results • Utilize unique FDA-Licensed LAL cartridges • Fully compliant to USP/EP/JP	• Rapid detection testing of cell samples • Using new concentration instrument • Results in 7 days • LOD – 1 CFU	• Rapid detection testing of cell therapies • Using new concentration instrument • Results in 3 days • LOD - <100 CFU	• MALDI-TOF and Sequencing Identification Services: most accurate methods, same day turnaround time, global coverage • In-sourcing MALDI-TOF Solution: most comprehensive library coverage.

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CHARLES RIVER C&GT 360° SOLUTIONS

Our integrated capabilities can support the entire development lifecycle

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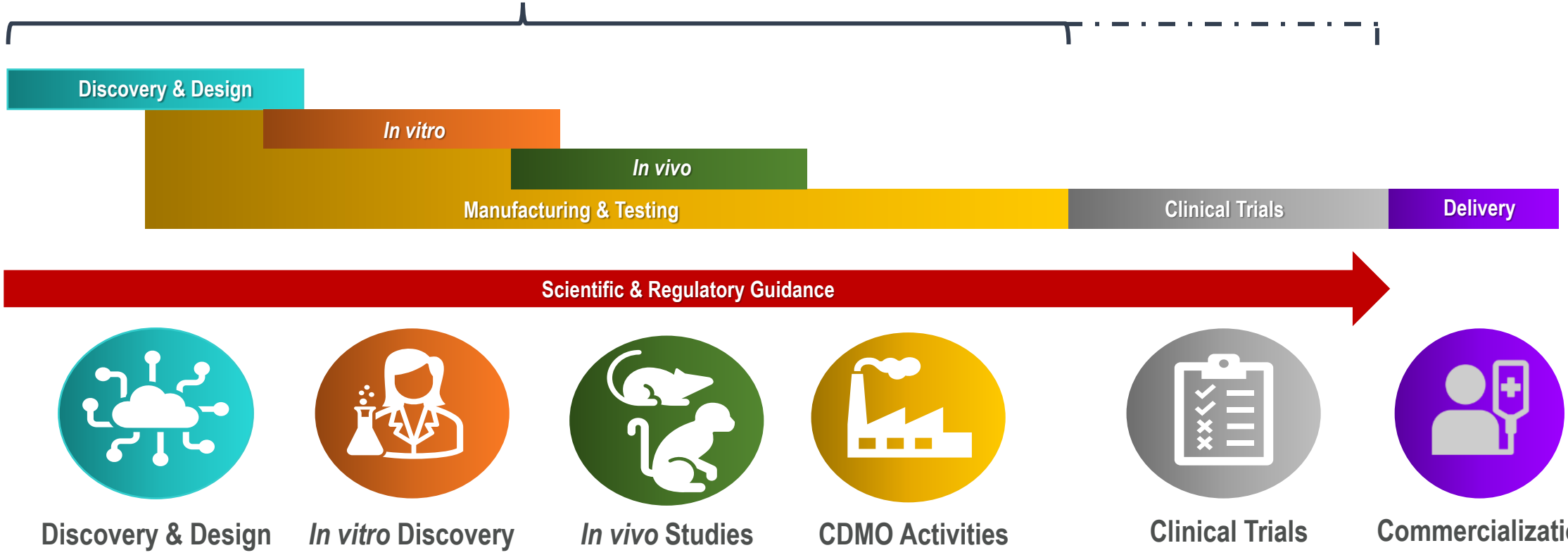
Accelerate and Achieve your C&GT Goals



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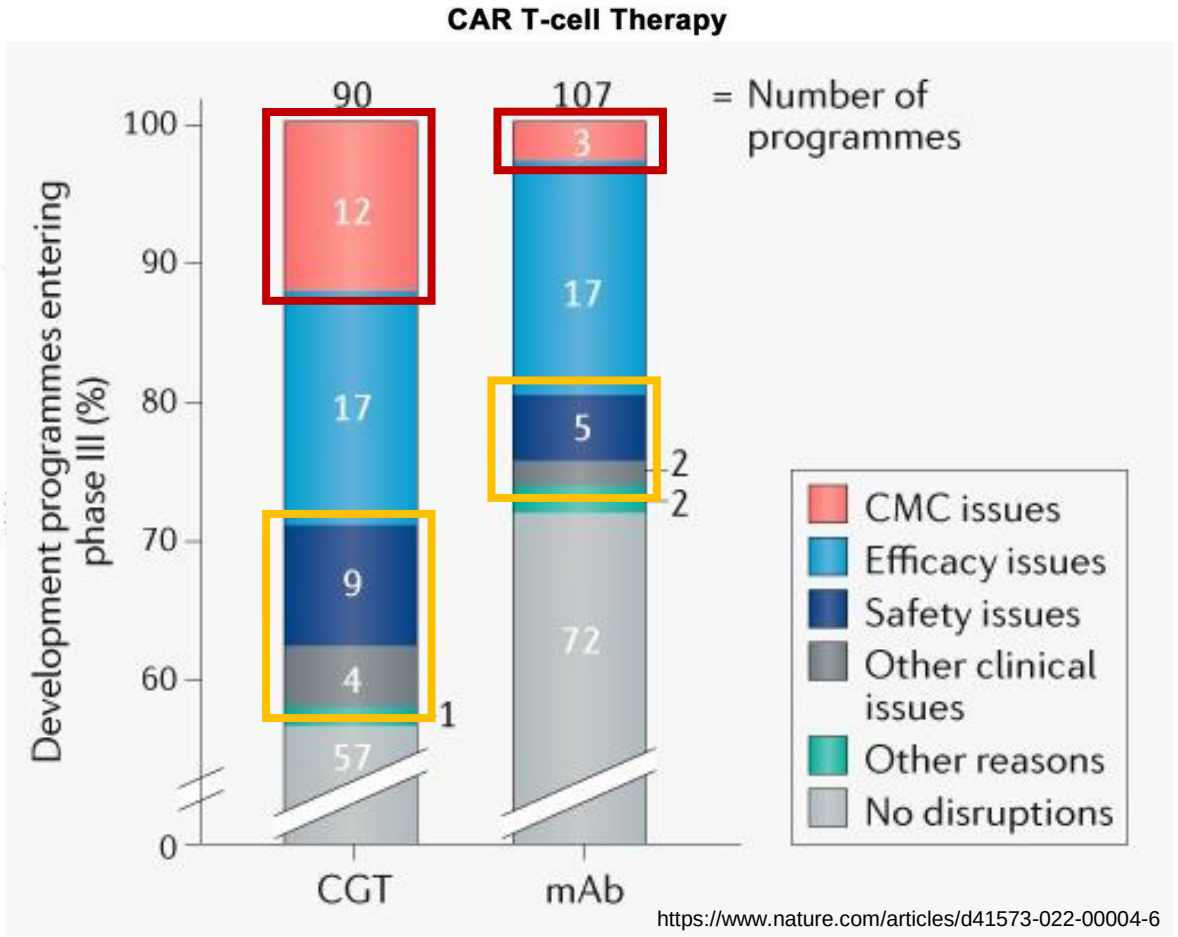
DEVELOPING A CAR-T CELL THERAPY WITH CHARLES RIVER

- Tissue acquisition (Donor PBMCs)
- Generate antibodies against antigen of interest
  - scFv/VHH/nanobody
- Target screening for binding affinity and specificity
- *In vitro* screening assays for on/off target pharmacology and functionality (cytokine/cytotox)
- In vivo models to assess biodistribution/efficacy & limited safety assessment end-points
- CDMO support for clinical & commercial
  - Starting Material Sourcing (Autologous & Allogeneic)
  - Process & Analytical Development
  - GMP Manufacturing



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CHARLES RIVER C&GT 360° SOLUTIONS

Multiple acquisitions and strategic partnerships strengthen our ability to service client needs

Discovery

Capabilities in targets, platforms, and therapeutic areas allow us to deliver data and insight you can trust to progress your drug discovery programs

distributed bio
a charles river company

Antibody Services; CAR-T, Bi-specifics, TCRs

scFv, VHH, Camelid libraries to create engineered immune cells for cell-based gene therapy programs (egCAR-T's)

- **On & Off target effects using cell microarr**
- **Off target modeling; Cytokine/Cytotox**
- **Model Selection /Pharmacology**
- ***In vivo* Efficacy**

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WE CAN FIND THE BEST scFv OR VHH FOR YOUR PROGRAM

Multiple complementary approaches to successful lead discovery

SuperHuman™ scFv Libraries

IgG, scFv,

CAR-T/NK/MAC, BiTE

Fully human scFv display libraries

Computationally optimized for sequence diversity and developability fitness

Proven track record of success, even against challenging targets

Obtain cross-species binders

COSMIC™ Antibody Library

IgG, scFv,

CAR-T/NK/MAC , BiTE

Newest & Largest library (100B unique sequence members)

Fully human CDRs with high rates of diversity, thermostability, non-immunogenicity

NEW Clone exclusivity

Tungsten™ Nanobody Libraries

VHH,

CAR-T/NK/MAC, BiTE

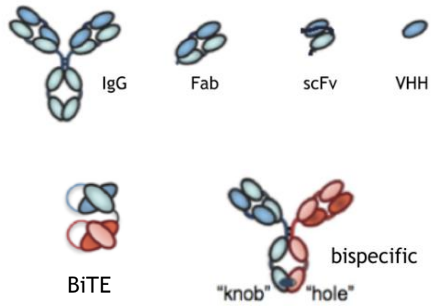
A camelid and a humanized VHH single domain library suitable for therapeutics, bispecifics, CAR-T/NK/MAC, reagents and diagnostics.

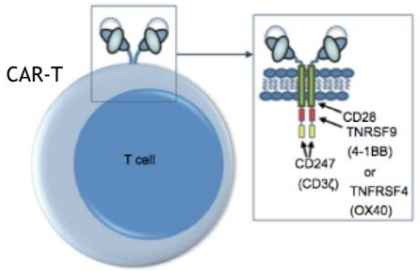
SLiC Single Light Chain scFv Library

Knob-and-Hole bispecifics

A SuperHuman™ Single Light Chain library enables rapid discovery of bispecific antibodies with an IGKV1-39 fully germline light chain.

A wide array of possible final formats





8 weeks to lead identification

Further optimize and de-risk with Tumbler platform

Royalty-free

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CHARLES RIVER C&GT 360° SOLUTIONS

Integrated cell and gene therapy safety assessment & laboratory support services

Unintended consequences in off target binding

Safety Assessment

We provide a full range of in vivo and in vitro testing and toxicology evaluations – across multiple sites – and offer comprehensive laboratory services. Supported by a vast network of specialty portfolio services:

In vitro

RETROGENIX™
A CHARLES RIVER COMPANY

Cell microarray technology for off-target screening; target deconvolution, receptor identification and CAR cell specificity; 6,350+ human expressed membrane and secreted proteins

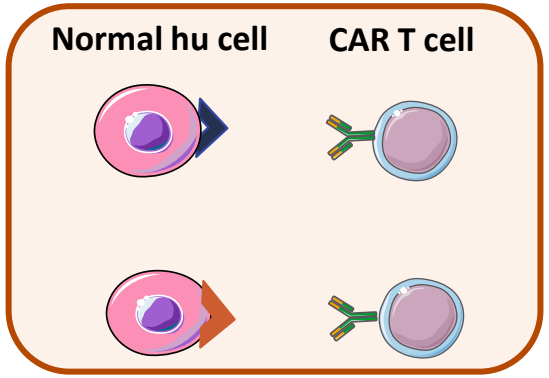
- **On & Off target effects using cell microarrays**
- **Tissue Cross Reactivity (TCR) IHC**

IN VITRO MODELING ON-TARGET AND OFF-TARGET EFFECTS

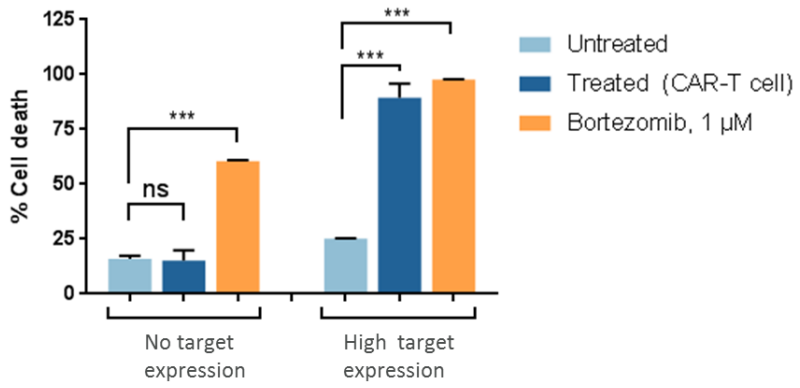
Functional cell-based assays: Cytokine; Cytotoxicity; Flow

- Assess risk of unwanted CART binding & killing
- T cell activation (IFNγ release)
- T cell-mediated cytotoxicity
- Compare lead CAR constructs to find balance between efficacy and safety
- Also suitable for TCR therapy studies; target donor cells can be screened for HLA type

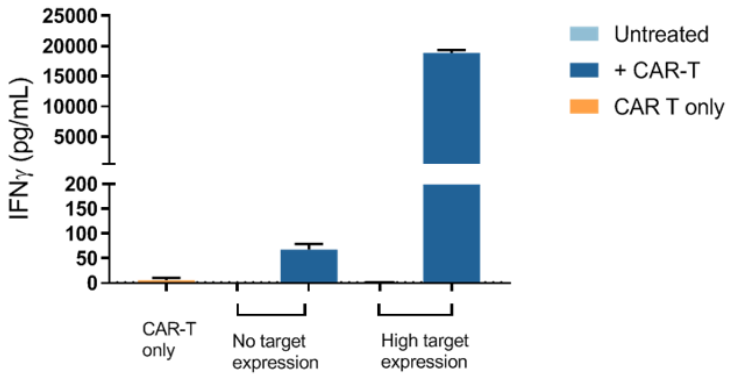
Unwanted reactivity

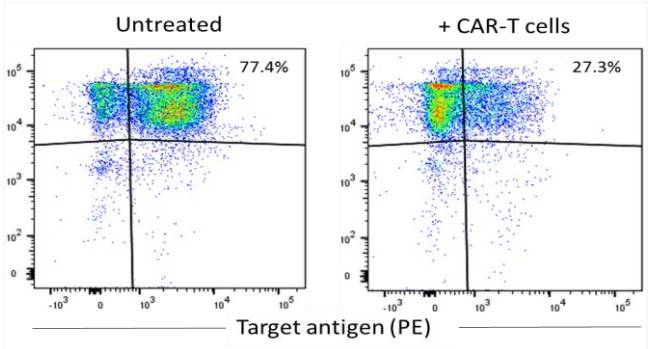


T cell mediated killing



CAR-T cell activation

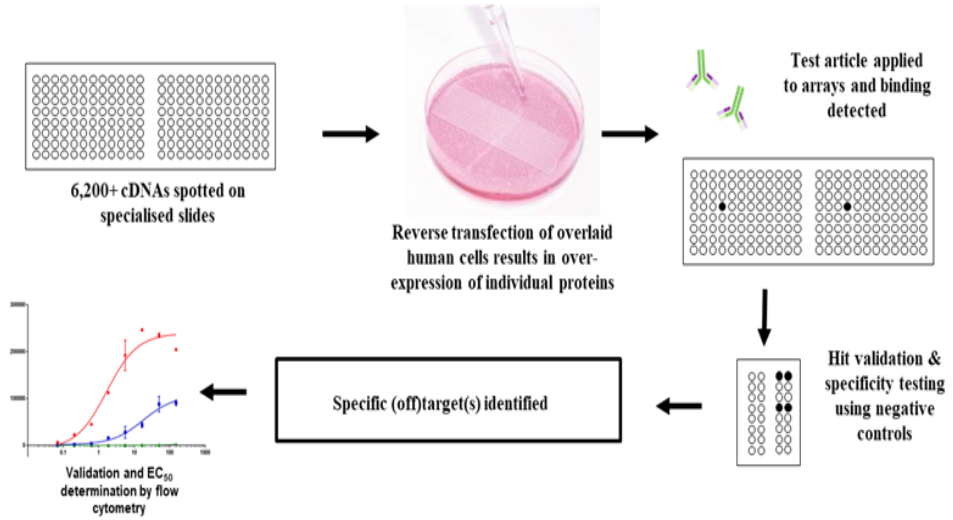




Targeted depletion of antigen expressing cells following co-culture with CAR T cells

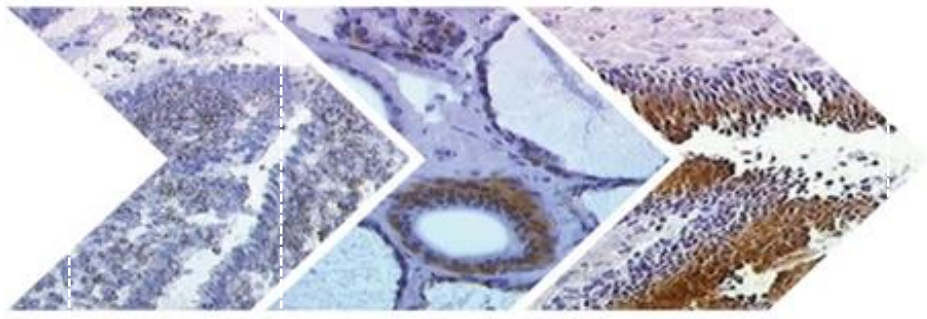
IN VITRO OFF-TARGET SAFETY ASSESSMENT

Cell Microarray Technology and IHC Human Tissues Cross Reactivity



Cell Microarray: Target specificity screening against 6,350+ membrane and secreted proteins

- Understand **off-target liability** of cell-based therapies, large, or small molecules
- cDNAs spotted; reverse transfected using human cells resulting in overexpression of individual proteins. Test article applied and binding detected
- **Lead candidate selection** – filter out polyreactive candidates at earlier stage
- IND-enabling specificity data - support IND and BLA submissions to FDA, EMA *



Immunohistochemistry-based Tissue Cross-Reactivity (TCR) Studies

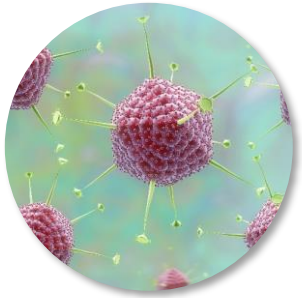
- Assess a **panel of 37 human tissues at 2 concentrations** to confirm distribution of target epitope and off-target binding
- Selection of tissue of interest for further in vitro safety assays
- 35 years of experience conducting ~100 TCR studies annually with >75% of those studies **conducted under GLP compliance for submission to regulatory agencies**.

*Retrogenix data used to support the licensing application for **Novartis' Kymriah**, the first CAR-T immunotherapy to receive FDA approval.

IN VITRO EFFICACY – GENE THERAPY

Understanding efficacy of gene therapies in *in vitro* platforms

Gene Therapy Vectors



The method of introducing therapeutic genes or drug materials into host cells to elicit a therapeutic benefit:

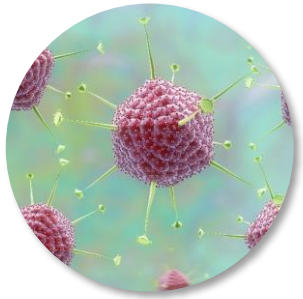
- Lentiviral vector
- Adenovirus vector
- Adeno-associated virus vector
- Oncolytic Viruses

Gene Editing Tools & Gene Payload

Targeted nucleases provide researchers with the ability to manipulate any genomic sequence for human gene therapy using these tools in cell line creation or animal models:

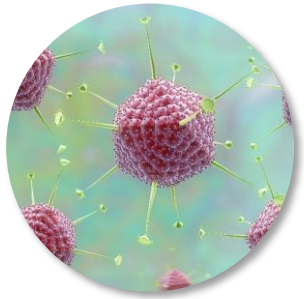
- CRISPR/ Cas9, ZFN's & TALENs
- cDNA & RNAi
- Plasmids
- Genetic Engineering of immune & stem cells

In vitro Activity



Vector Selection and Delivery Method:

- Vector tropism
- Promoter, transgene product, etc.
- Surrogate product
- Delivery system



Gene Therapy vectors and transgene testing:

- iPSCs
- Patient–derived cells
- Commercial Cell lines
- Custom cell lines

CHARLES RIVER CGT 360° SOLUTIONS

Integrated cell and gene therapy safety assessment & laboratory support services

Characterization/specificity

Safety Assessment

We provide a full range of in vivo and in vitro testing and toxicology evaluations – across multiple sites – and offer comprehensive laboratory services. Supported by a vast network of specialty portfolio services:

In vivo

- **Bioanalytical Methods**
- **Biodistribution**
- **Immunogenicity**
- **Toxicology**
- **Pathology**

ANIMAL MODELS TO EVALUATE CELL PHARMACOLOGY

Selecting the appropriate animal model and understanding their uses and limitations

Monkey CAR T (specific for human TAA)

Monkey immune cells

Uses	Limitations
• Similarity with human • NHP is immune competent • May replicate clinical toxicity better than rodents eg., CRS, neurotoxicity	• Expensive/CRO needed • No tumor present • Small cohort size • Very limited set of studies

Mouse CAR T (specific for human TAA)

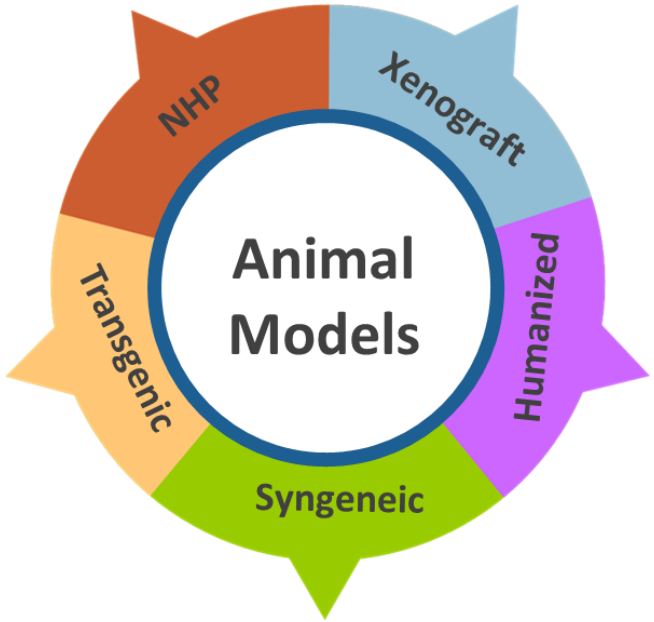
Mouse immune cells

Mouse tumor

Mouse normal tissue/cells

Human TAA

Uses	Limitations
• Human target antigen expression in immunecompetent host • Evaluation of off-tumor effects on healthy tissue	• Mouse biology • Breeding to create Tg mice • Studies don't always predict off-tumor toxicity



Mouse CAR T

Mouse Immune cells

Mouse tumor

Mouse TAA

Uses	Limitations
• Mouse CAR T cells evaluated in a fully functional mouse immune system • Models can reveal on-target off-tumor toxicity • No xenoreactivity	• Limited insight into mechanisms of human CAR T • CRS limited and strain-specific

Human CAR T

Human tumor

Human TAA

Used For	Limitations
• Proof of concept/identify leads • Dose/activity relationship • evaluate CAR design • Biodistribution and persistence • Provide some safety information	• Absence of host immune cells • Requires expression and crossreactivity with mouse target • Limited CRS/immunosuppression • GVHD

Human CAR T

Human immune cells

Human tumor

Human TAA

Uses	Limitations
• CAR T cells evaluated in the presence of additional human immune cells	• Humanization process is complex and engraftment favors T&B cells, myeloid cells under represented

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GENE AND CELL THERAPIES ACROSS THE CONTINUUM

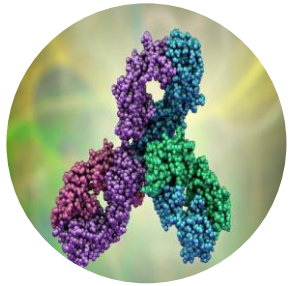
In *vivo* pharmacology and Safety Assessment

Model Selection

Selecting the Right Species & Route of Administration

- *Rodent vs NHPs*
- *CNS, Ocular and autoimmune models*
- *Immunosuppressed & humanized models*
- *Surgical models*
- *Various delivery routes to mimic clinical delivery*

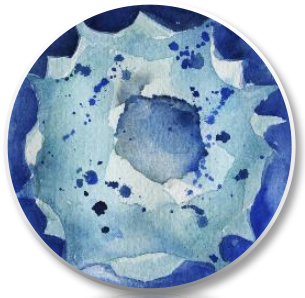
In Vivo Efficacy



Proof of Concept & Primary Pharmacology

- Biologic Effect
- Mechanism of Action
- Primary Pharmacology
- Tissue/cell engagement
- Duration of effect
- Animal-specific surrogates

Bioanalytical Methods



Platforms for cell and gene therapy program

- Immunohistochemistry
- Antibody screening/Neutralizing antibody assays
- ddPCR/qPCR
- Flow cytometry
- Cytokines
- ELISpot

BIODISTRIBUTION – CELLULAR THERAPIES

Where does it go, how long does it stay?

Survival/Persistence

- Endurance of the cell in the animal model
  - Use of pharmacology models to assist in PK modelling and dose prediction.
- Association of persistence with efficacy
- Effects on persistence, potency and durability
  - local tissue environment
  - method of administration

Differentiation

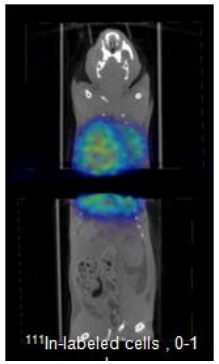
- Phenotypic or genotypic stability
- Undesired cell types
- Uncontrolled cell proliferation (tumorigenicity)

Migration/Organ Distribution

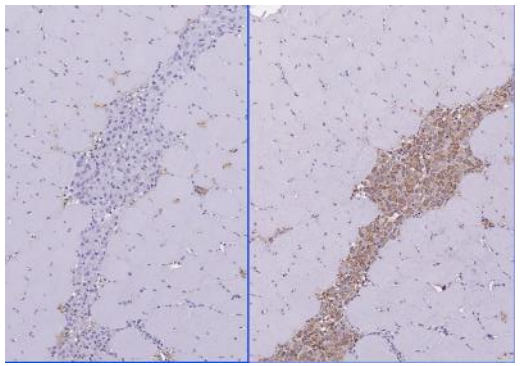
- Target / non target tissues - systemic distribution
- Tracking persistence, using qPCR and ddPCR

Translational Imaging

- Magnetic resonance and translational nuclear imaging (PET and SPECT) from mouse to non-human primates to clinic
- Large and small animal *in vivo and ex vivo* imaging
- Comprehensive imaging data management, analysis and reporting



in vivo imaging



Immunohistochemistry

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BIODISTRIBUTION – GENE THERAPIES

Distribution, Peak Expression, Duration of Effect?

An essential part of Safety Assessment

- Influences animal species selection
- Impacts study duration and time points
- Aids in the interpretation of pharmacology and toxicology data

Include core tissues and program specific

- Blood, injection site, brain, spinal cord , liver, kidney, heart, spleen, adrenal grands (high blood flow tissues)
- Tissues indicated by route of administration
- Tissues indicated by vector tropism

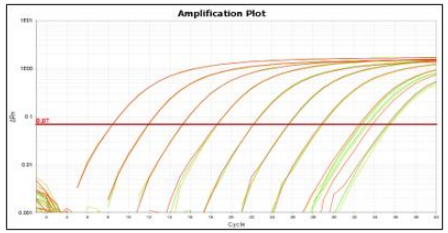
Address acute effects, peak exposure/expression, and persistence

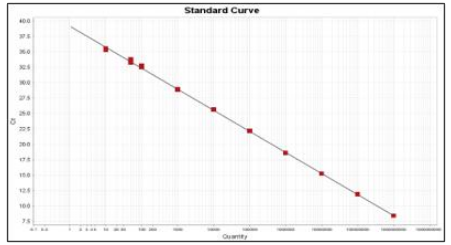
- Multiple in-life time points and terminal endpoints
- Quantification of genetic material (vector and transgene) and expressed product (protein)
- Duration of pharmacology and toxicology studies may differ

Standard and program-specific bioanalytical approaches

- Vector-specific assays; e.g., AAV genome/subtype, by qPCR/ddPCR
- Quantitative analysis of mRNA by RT-PCR/ddPCR
- Protein analysis by ELISA, MSD, Gyros, other

QuantStudio 5 & 7 Flex Real-Time PCR Systems, Applied Biosystems





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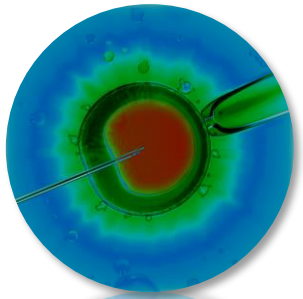
SAFETY CONSIDERATIONS – CELL AND GENE THERAPY

Platforms, Technologies and Nucleic Acid Based Therapeutics

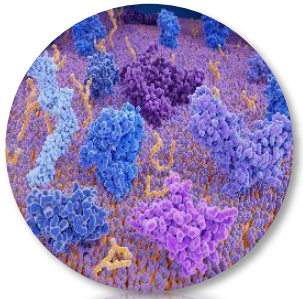
Immunogenicity



Approaches and Considerations

- Humoral and cell mediate immunity
- Immune suppression
- Pre-existing immunity
- Immune activation by the vector/transgene
- Pre-clinical vs. clinical assessments

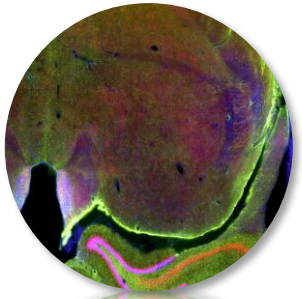
Safety Assessment



Selecting the Critical Endpoints for Evaluation

- Standard safety assessment modified for program-specific need
- Biodistribution to target and non-target tissues
- Expression of the transgene and transgene product activity

Pathology



Safety Assessment Techniques:

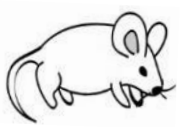
- Clinical and molecular pathology
- Neuropathology
- Specialized microscopy
- Immunohistochemistry
- In situ hybridization
- Specialized stains/techniques
- Digital pathology partnership

TUMORIGENICITY CONSIDERATIONS – CELLULAR THERAPIES

Stem Cell or CAR-T Therapy

Clinical route administration

Maximum feasible dose



Immuno-compromised rodent

Duration
3-6 months

- Clinical observations and body weights
- Evaluate for tumor presence
- Tissues retained for histopathology and/or aseptic PCR

- Case by case study design/justification
- Recommendations based on individualized risk assessment for each therapy
- Clinical route of administration / Effect of microenvironment
- Maximum feasible dose
- Immunocompromised rodent
- *in vitro* assessments in place of *in vivo* studies where appropriate

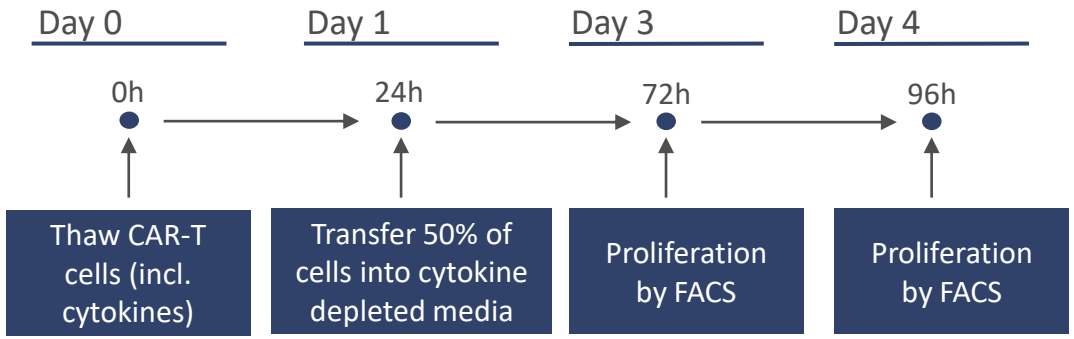
CYTOKINE DEPENDENCY ASSAY

Genotoxicity evaluation

Assess effects of potential insertional mutagenesis on CAR-T cell survival, maintenance and proliferation

To confirm that proliferation of the CAR-T cells under cytokine culture conditions is solely due to presence of cytokines and not due to negative effects of the gene editing causing hyper proliferation, their cytokine dependency will be tested

- CAR-T cells will be thawed and cultured in standard T cell media containing cytokines for 24 hours
- At 24 hours, 50% of the CAR-T cells will be cultured with cytokine depletion media (absent of any cytokines) where 50% will continue to be cultured with standard cytokines containing T cell media for a further 48 and 72 hours
- T cell proliferation will be assessed by flow cytometry utilizing the Cell Trace Proliferation kit
- Cell count and viability will be also be collected as read-out
- Readout will be taken at both 48 and 72 hours post cytokine depletion



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LABORATORY SERVICES/CAPABILITIES

Supporting preclinical and clinical needs

SAMPLE RECEPTION & BIOBANKING

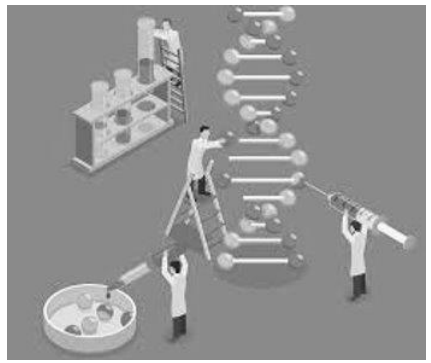
- GLP and GCP compliance
- On site data privacy officer
- Storage in secured buildings with temperature controlled equipement and back-up freezers
- Large storage capacity (17 x -80°C freezers)
- Biobanking
- Support for multisite and multi-country clinical programs

SAMPLE PREPARATION

- Nucleic acids extraction
- **DNA, RNA, mRNA,** from numerous sources
  - **Frozen tissues & cells** (organs, animals and humans)
  - **Blood**
  - **Biological fluids & swabs**
  - **FFPE samples**
  - **Limited sample quantities**

HIGH THROUGHPUT SAMPLE ANALYSIS

- **ddPCR**, **qPCR**, **RT-qPCR**
- Ligand Binding Assays
- Scientific expertise to support your biomarker strategy



DATA QC & ANALYSIS

- **QC'd data**
- **QA'd data**
- **Non-GLP Report**
- **GLP Report**
- **Expedited analysis timelines can be discussed at the initiation of programs**

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CHARLES RIVER CGT 360° SOLUTIONS

Transition seamlessly into human trials with our integrated clinical support capabilities

Clinical Support

We provide a full range of clinical support services when time comes to enter human trials. We easily transition with you from the pre-clinical to clinical phase of development

- **Bioanalysis**
- **Immuno-phenotyping**
- **Molecular biology to biomarkers**
- **Sample management**
- **Clinical kitting**

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CHARLES RIVER CGT 360° SOLUTIONS

Integrated cell and gene therapy research model solutions

Research Models and Services

Immunodeficient Animal Models

Development and expansion of humanized models (PBMC, and CD34+) for human cell engraftment/transfer to generate human immune models for cell therapy studies

Genetically Engineered Models and Services

Generate transgenic models and facilitate model development through CRISPR and RNAi technologies for gene therapy

AAV Neutralization Antibody Testing

RUO/non-GLP serology and PCR-based antibody screening assays for pre-exposure to viral vectors in NHPs being qualified for gene therapy studies.

RESEARCH MODELS & SERVICES

Integrated cell and gene therapy research model solutions

Our extensive portfolio of research animal models and services along with our global network of commercial breeding facilities; rigorous genetic standards; and core values of animal welfare, biosecurity, and the 3Rs uniquely position us to support C&GT development.

Research Animal Models

NCG & Immunodeficient Models

- NCGs are triple immunodeficient models lacking functional T, B and NK cells with the ability to host xenograft cells, tissue and human immune system components
- Support human cell engraftment/transfer to generate human immune models for cell therapy studies

Humanized Models

- Off-the shelf NCG models immuno-humanized with PBMC and CD34+ immune cells for translational research

Genetically Engineered Models and Services

Transgenic Model Creation

- Create, customize, select and maintain transgenic models through CRISPR/Cas9 technologies for gene therapy
- Generate Knock-in and Knock-out mice to study gene function and human disease within transgenic models

Contract Breeding Services

- Full service, colony management program for genetically engineered animals including breeding and animal holding, quarantine, IVF expansion, line recovery, and more.

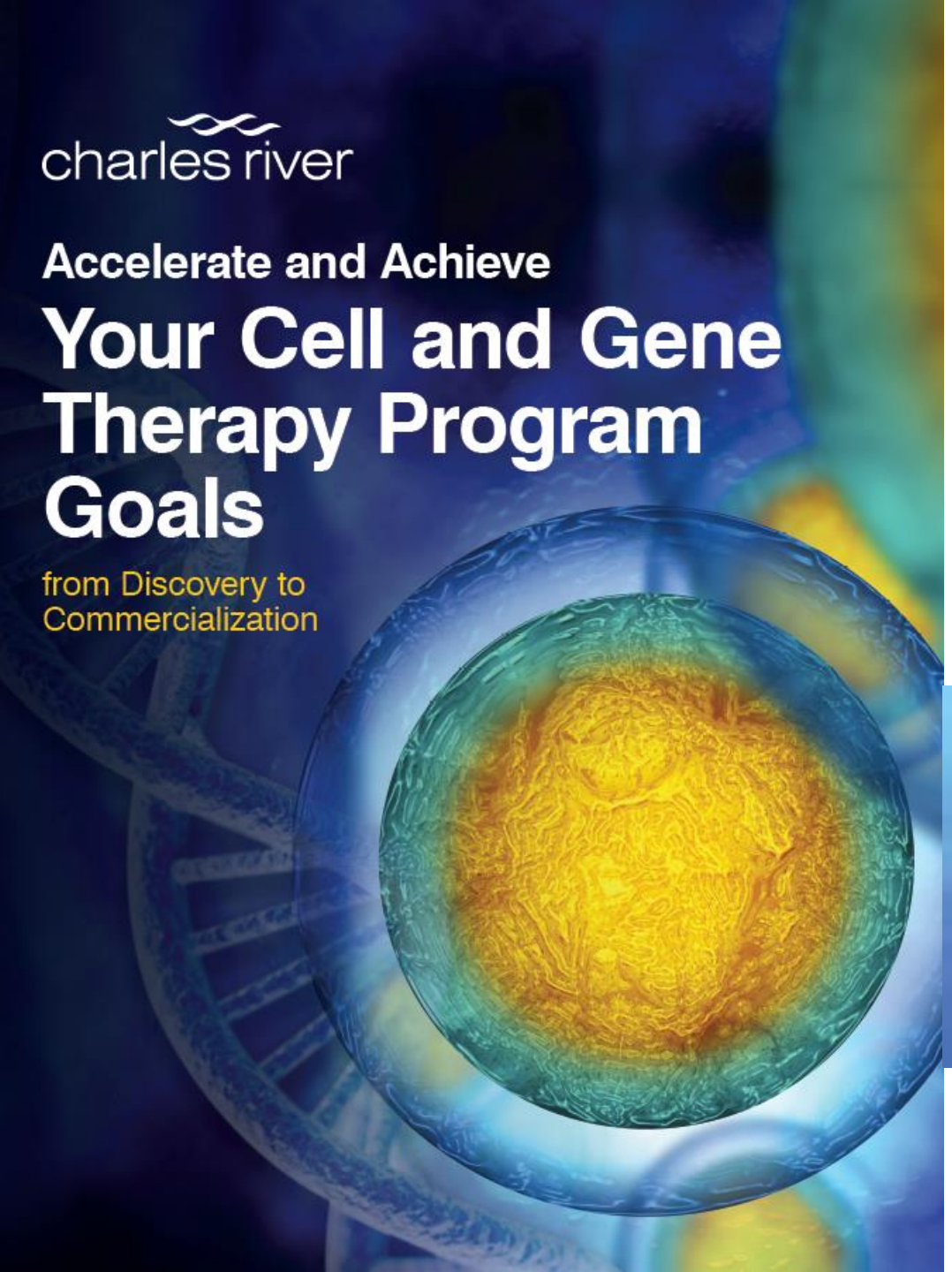
Non-GXP Testing Solutions

AAV Neutralizing Antibody Testing

- RUO/non-GLP serology and PCR-based antibody screening assays for pre-exposure to viral vectors in NHPs being qualified for gene therapy studies.

Cell Line/Research Biologics Screening

- Screening of rodent research biologics via CLEAR PCR panels to ensure animal colonies are free of infectious agents and confirm origination from specified host species



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Thank you

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