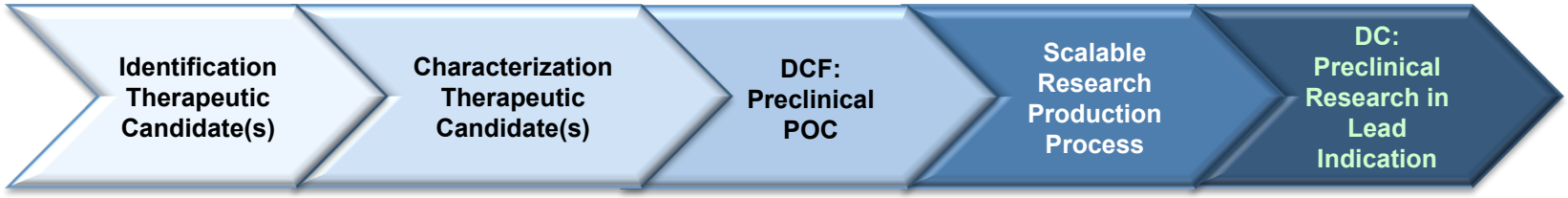
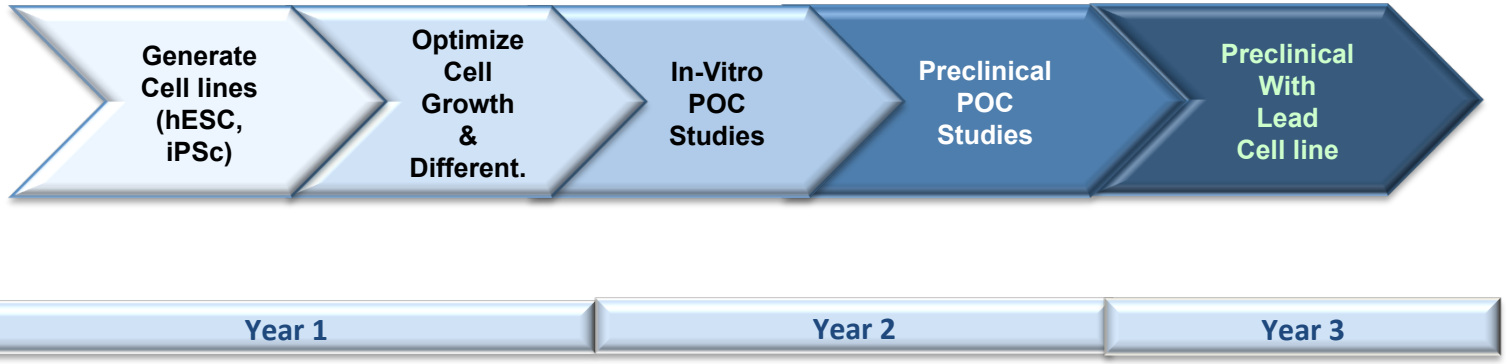
RFA 11-02 Appendix A

In Scope Activities: Cell Therapy Development



Cell Line Selection	POC Studies	Disease Modifying Studies
• Define cell source (GTP compliant), optimize culture growth conditions for cell lines, generate research cell bank(s) • Develop robust differentiation method to the desired lineage • Develop assays to characterize cell population (e.g. identity, purity, stability) • Define cell line selection criteria (e.g. differentiation efficiency and activity, genomic stability and scalability) • Pilot MOA and potency studies	• Select lead GMP/GTP compatible cell lines for POC preclinical studies • Demonstrate therapeutic activity in at least one disease model with at least one cell line (in-vitro and in-vivo) • Demonstrate in-vivo activity: show histology, regenerative tissue, graft survival, migration etc. • Develop methods to deliver cells to target tissue	• Demonstrate reproducible disease modifying activity with GMP/GTP compatible lead cell line in relevant disease model(s) • Address in-vivo activity: e.g. cell engraftment, proliferation, differentiation, graft survival, migration etc. • Define therapeutic dose, and conduct pilot safety, stabilities studies • Perform research scale process development • Develop clinical strategy plan

Example of milestones and success criteria for Cell therapy



Example of milestones and success criteria for cell therapy DC Award:

1. Select Pluripotent (PSC) line – Derive and characterize therapeutic cells:

- Define cell source and optimal growth and expansion conditions
- Optimize differentiation to the target lineage and characterize cell population (e.g. identity, purity)
- Elect pluripotent parental cell line based on defined selection criteria (e.g. genetic stability, differentiation efficiency, and scalability)

Success criteria: *Select GMP compatible cell line(s) that are reproducibly differentiated to the x % of the desired linage and can be expanded in a scale sufficient to support preclinical POC studies while maintaining a normal karyotype*

2. Conduct POC preclinical studies with elected cell line (s):

- Demonstrate therapeutic activity in at least one disease model with at least one cell line

Success Criteria: *Therapeutic activity should be defined as % improvement in a disease read out compared to control/sham treatment*

3. Demonstrate disease modifying activity with GMP compatible lead cell line in a relevant disease model:

- Generate GTP/GMP compatible cells at scale and differentiation efficiency sufficient to support reproducible disease modifying studies
- Define therapeutic cell dose and demonstrate reproducible, and statistically significant disease modifying activity in a relevant disease model using GTP/GMP compatible cells
- Conduct preliminary safety and histological assessment of treated animals (e.g. survival, cell related toxicity, tumor and/or off target tissue formation, and engraftment of desired cells)

Success Criteria: 1) *Produce GMP compatible small-medium research scale to support reproducible disease modifying studies (e.g. x number of cells in x% purity* ***2)*** *Therapeutic activity should be defined as % improvement in a disease read out compared to control/sham treatment*

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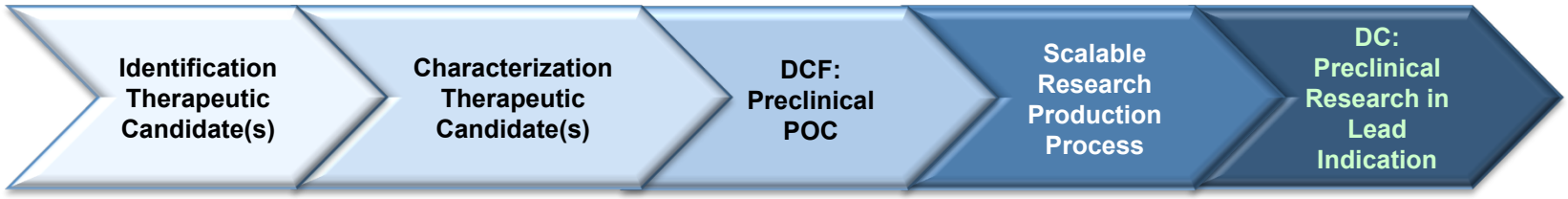
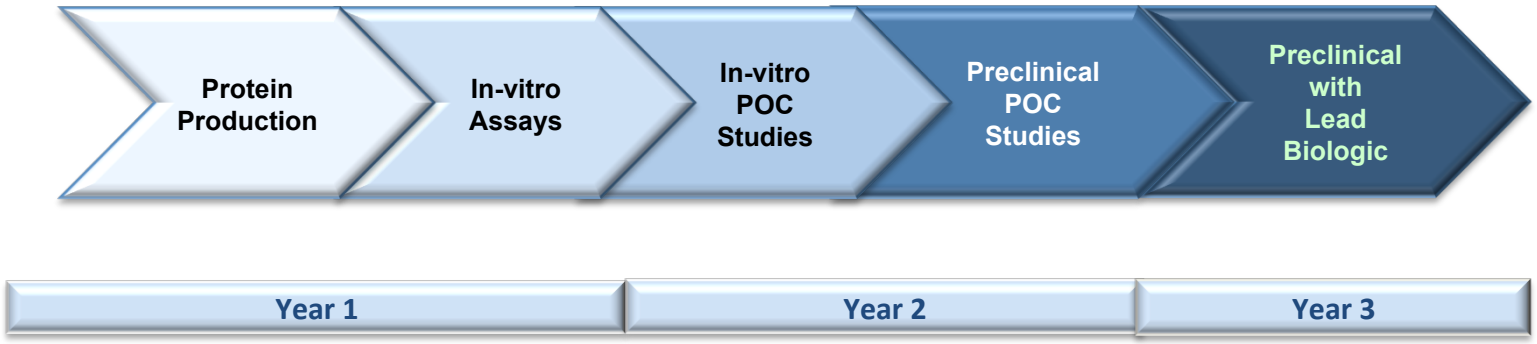
In Scope Activities: Biologic Therapy Development



Characterization and Production	POC Studies	Disease Modifying Studies
• Optimize scalable repeatable production process of human recombinant protein in appropriate system • Determine and document yield, purity, stability, specific activity, IC50, and other features if available • Optimize liposomal packaging/scaffold (if necessary) • Characterize the biochemical properties of produced protein	• Demonstrate POC therapeutic activity with lead human recombinant protein in at least one disease model in-vitro and in-vivo • Develop scalable research production process to support preclinical studies • Initiate dose escalation studies to identify maximum tolerated dose and drug related toxicity	• Demonstrate disease modifying activity with human lead recombinant protein in relevant disease model(s) • Address in-vivo activity: bio availability, clearance and pharmacology • Define therapeutic dose and conduct pilot safety studies • Perform research scale process development • Develop clinical strategy plan

Example of milestones and success criteria for Biologic therapy



Example of milestones and success criteria for biologic therapy DC Award:

Generate sufficient amounts of human recombinant protein to support pre-clinical POC studies:

- Optimize scalable repeatable production research process of human recombinant protein in appropriate system (e.g. in CHO Cells)
- Optimize liposomal packaging/scaffold if necessary for protein administration
- Characterize and document the biochemical properties of produced protein: purity, specific activity, specificity, IC50, other features if available e.g. affinity to target receptor etc.
- Generate GMP compatible cell line to produce human recombinant protein in a reasonable research scale to support preclinical studies

Success Criteria: Develop a small to medium research production scale to make a reasonable yield, highly pure, potent, and stable human recombinant protein

***2. Conduct POC preclinical studies with* human recombinant protein :**

- Demonstrate a dose dependent therapeutic activity in at least one disease model with human lead recombinant protein
- Initiate dose escalation studies to identify maximum tolerated dose and drug related toxicity

Success Criteria *Therapeutic activity should be defined as % improvement in a disease read out compared to control/sham treatment*

3. Demonstrate disease modifying activity with lead human recombinant protein in a relevant disease model:

- Generate GTP/GMP compatible recombinant protein at scale sufficient to support reproducible disease modifying studies
- Define therapeutic dose and demonstrate reproducible, statistically significant disease modifying activity in a relevant disease model using GTP/GMP compatible recombinant protein
- Conduct preliminary safety assessment in vivo (e.g. toxicity, off target effect).

Success Criteria: 1) *Develop GMP compatible small-medium research scale to support preclinical studies (e.g. protein yield xmg/l, purity x%*

2) *Therapeutic activity should be defined as % improvement in a disease read out compared to control/sham treatment (e.g. reproducible and safe)*

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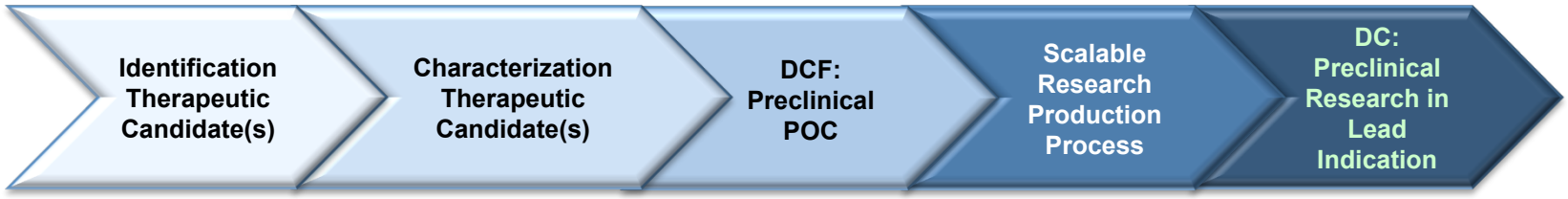
In Scope Activities: mAb Therapy Development



mAb Generation and Selection	POC Studies	Disease Modifying Studies
• Produce sufficient amount of recombinant antigen • Immunize mice and generate antibodies • Develop ELISA and FACS assays for mAb screen • Assess purity, potency and species cross reactivity of selected mAb(s)	• Determine the selectivity, specificity and avidity of selected lead mAb(s) • Generate GMP/GTP compatible cell line to produce mAb(s) for POC preclinical studies • Demonstrate therapeutic activity in at least one disease model with at least one mAb (in-vitro and in-vivo) • Generate expression cell line to produce chimeric lead mAb(s)	• Demonstrate reproducible disease modifying activity with lead chimeric/humanized mAb(s) in a relevant disease model(s) • Address in-vivo activity: bio availability, clearance and pharmacology • Define therapeutic dose and conduct pilot safety studies • Perform research scale process development • Develop clinical strategy plan

Example of milestones and success criteria for mAb therapy

Example of milestones and success criteria for mAb therapy DC Award:

1. Generate Antigens for immunization and initiate immunization *:*

- Produce sufficient amounts of recombinant antigen of maximum 3-4 targets and 3 different antigens/target
- Initiate Immunization in mice (e.g. 6 mice/antigen)
- Develop ELISA and FACS assays for mAb/hybridoma screen
- Generate hybridoma and screen in ELISA assay to identify "hits" that cross react with the mouse and cynomolgus orthologous
- Select positive "hits" mAb(s)

Success criteria*: identify at least one "hit" mAb that binds the corresponding target in Elisa and FACS assays*

2.Conduct POC preclinical studies with elected mAb(s) :

- Determine the selectivity, specificity and avidity of lead murine mAbs
- Functional analysis: cytotoxic-CDC and ADCC assays, biological activity, cellular MOA studies
- Conduct POC studies in-vivo with 1-3 lead murine mAb(s)
- Chimerize 1-3 lead murine mAbs to generate human/mouse chimera

Success Criteria: *Elect a lead mAb(s) with the appropriate avidity (nM range) to target the corresponding antigen with the desired functional activity (e.g. Inhibitory, modulatory, cytotoxic). Conduct preclinical studies with 1-2 lead murin and chimeric mAb(s)*

3. Demonstrate disease modifying activity with lead mAb in a relevant disease model

- Generate GTP/GMP compatible chimeric/humanized mAb at scale sufficient to support reproducible disease modifying studies
- Define therapeutic dose and demonstrate reproducible, statistically significant disease modifying activity in a relevant disease model using GTP/GMP compatible recombinant mAb(s)
- Conduct preliminary safety assessment in vivo (e.g. toxicity, off target effect).

Success Criteria: 1) *Develop GMP compatible small-medium research scale to support preclinical studies (e.g. mAb yield xmg/l, purity x%* ***2)*** *Therapeutic activity should be defined as % improvement in a disease read out compared to control/sham treatment (e.g. reproducible and safe)*

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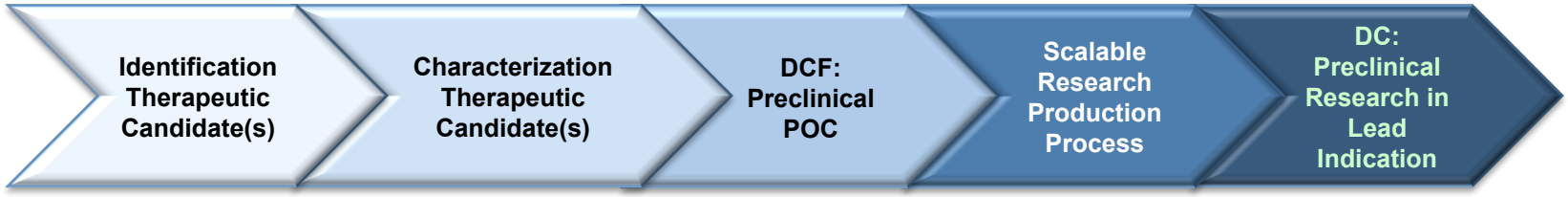
In Scope Activities: Small Molecule Therapy Development



Selection of "Hits"

- Develop biochemical and/or cell based assay for small molecule drug screen (e.g. potency and selectivity)
- Format the selected assay into HTS format
- Perform HTS chemical library screen to identify "hits" (low μM range)
- Develop assays to evaluate potency selectivity, reversibility and MOA
- Select "hits" for further characterization

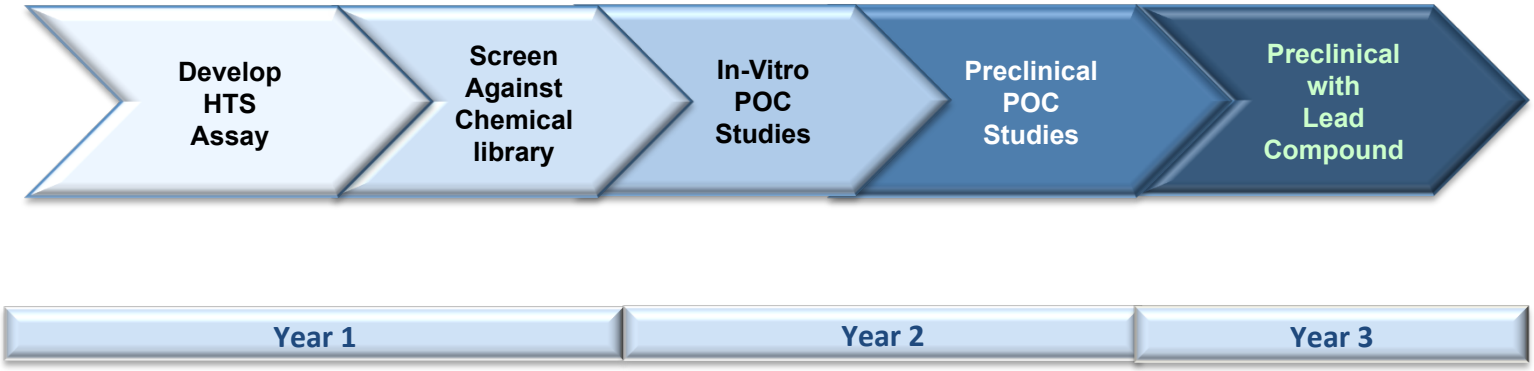
POC studies

- Demonstrate therapeutic activity in at least one disease model with at least one "hit" (in-vitro and in-vivo)
- Lead optimization: Initiate limited medicinal chemistry effort against 2-3 "hit" series to determine SAR
- Identify a lead (s) with IC50 in the nM range

Disease Modifying Studies

- Demonstrate reproducible evidence of dose dependent disease modifying activity with lead compound(s) (in-vitro and in-vivo)
- Address in-vivo activity: e.g. pharmacology, bioavailability, and half life of lead in-vivo
- Define therapeutic dose, and conduct pilot safety stabilities studies
- Perform research scale process development
- Develop clinical strategy plan

Example of milestones and success criteria for small molecule therapy



Example of milestones and success criteria for small molecule therapy DC Award:

Develop HTS Assay for small molecule screen:

- Develop biochemical and/or cell based readout for drug screen
- Format selected assay into HTS screen
- Screen chemical library to identify hits inhibitors (>μM range)
- Select "hits" (low μM range) for further characterization: dose response, determine IC50, specificity and selectivity

Success Criteria: *Elect "Hit(s)": identify 1-3 series of chemical compounds that modulate the desire cell or biochemical effect at low μM range*

2.Conduct POC preclinical studies with elected "hit"(s):

- Conduct POC studies with selected "hits" on cellular function and in-vivo preclinical models
- Lead optimization: Initiate limited effort of chemistry against 2-3 series to determine SAR
- Identify a lead(s) with IC50 in the nM range

Success Criteria: *elect a lead molecule with IC50 in the nM range with in-vitro and in-vivo activity*

3. Demonstrate disease modifying activity with lead small molecule in a relevant disease model:

- Synthesis sufficient amount of lead small molecule to support reproducible disease modifying studies
- Define therapeutic cell dose and demonstrate reproducible, statistically significant disease modifying activity in a relevant disease model with lead small molecule
- Conduct preliminary safety assessment in vivo (e.g. toxicity, off target effect, PK and clearance).

Success Criteria: 1) *Synthesis a research scale small molecule to support preclinical studies (e.g. xmg, x% purity* ***2)*** *Therapeutic activity should be defined as % improvement in a disease read out compared to control/sham treatment (e.g. reproducible and safe)*