iSBTc Oncology Biologics Development Primer

February 28-29, 2008

Argos™ THERAPEUTICS

Dendritic Cell Based Products

RNA electroporated CD14-derived Dendritic Cells

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Overview

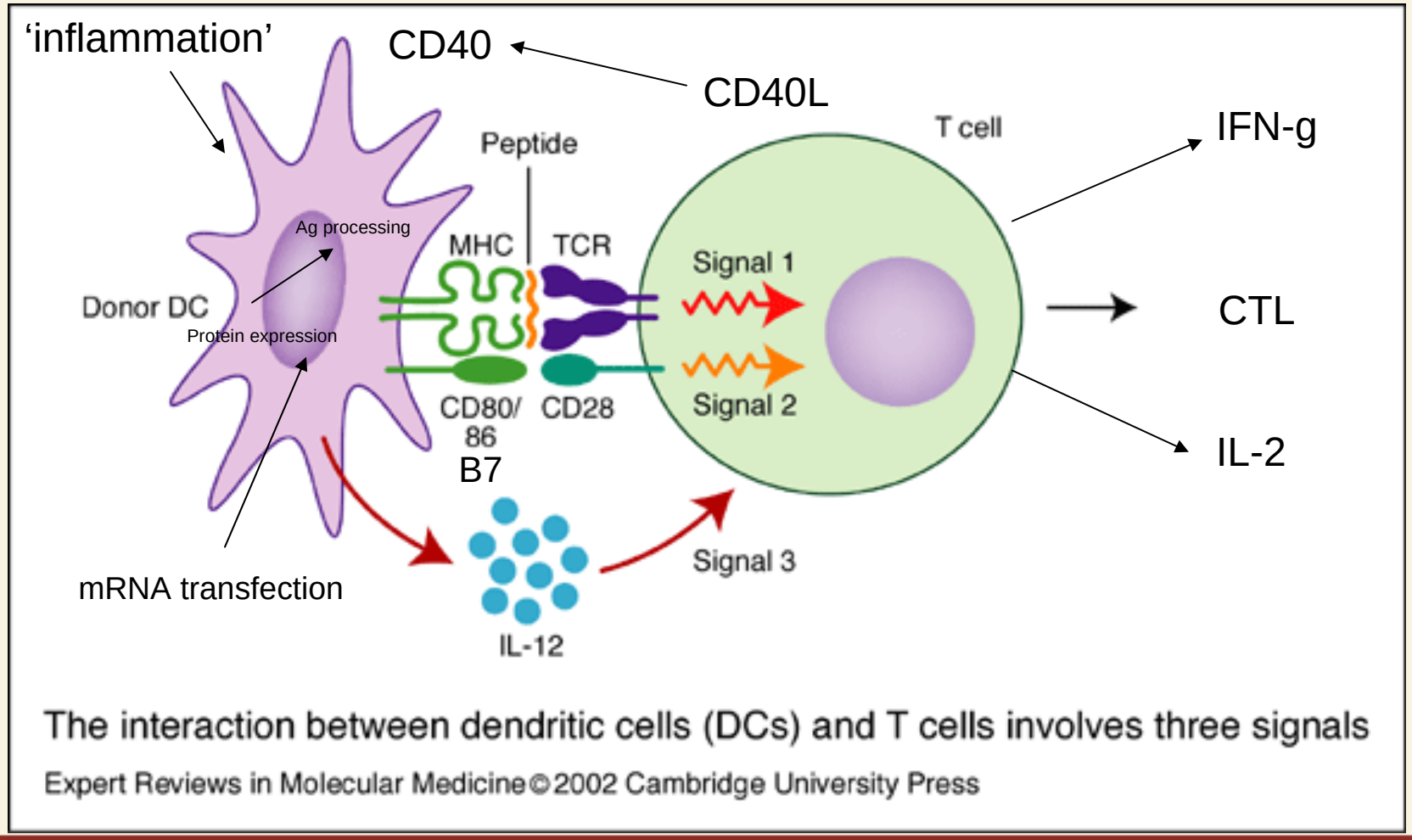
- Introduction to DCs and Arcelis™
- Issue 1: Non-Clinical Package
- Issue 2: Phase 1 Considerations
- Issue 3: Translational Package
- Issue 4: Product Optimization
- Issue 5: Suitable Study Designs
- Issue 6: Combination Therapy
- Issue 7: cGMP Manufacturing
- Discussion

Dendritic cells (DCs):

- **Link between innate and adaptive immunity**
- Organize and transfer information from the outside world to the cells of the adaptive immune system
- Versatile controller of the immune system
- **Peripheral monocyte or bone-marrow-derived**
- **Immature - self tolerance**
- **Mature – induction of antigen specific immunity**
- **Impaired DC function leads to or associated with:**
  - **Autoimmunity: lupus, arthritis, psoriasis**
  - **Allergy**
  - **Cancer**

Dendritic Cell – T-cell:

Interaction between innate and adaptive immunity facilitated by IL-12



The interaction between dendritic cells (DCs) and T cells involves three signals

Expert Reviews in Molecular Medicine©2002 Cambridge University Press

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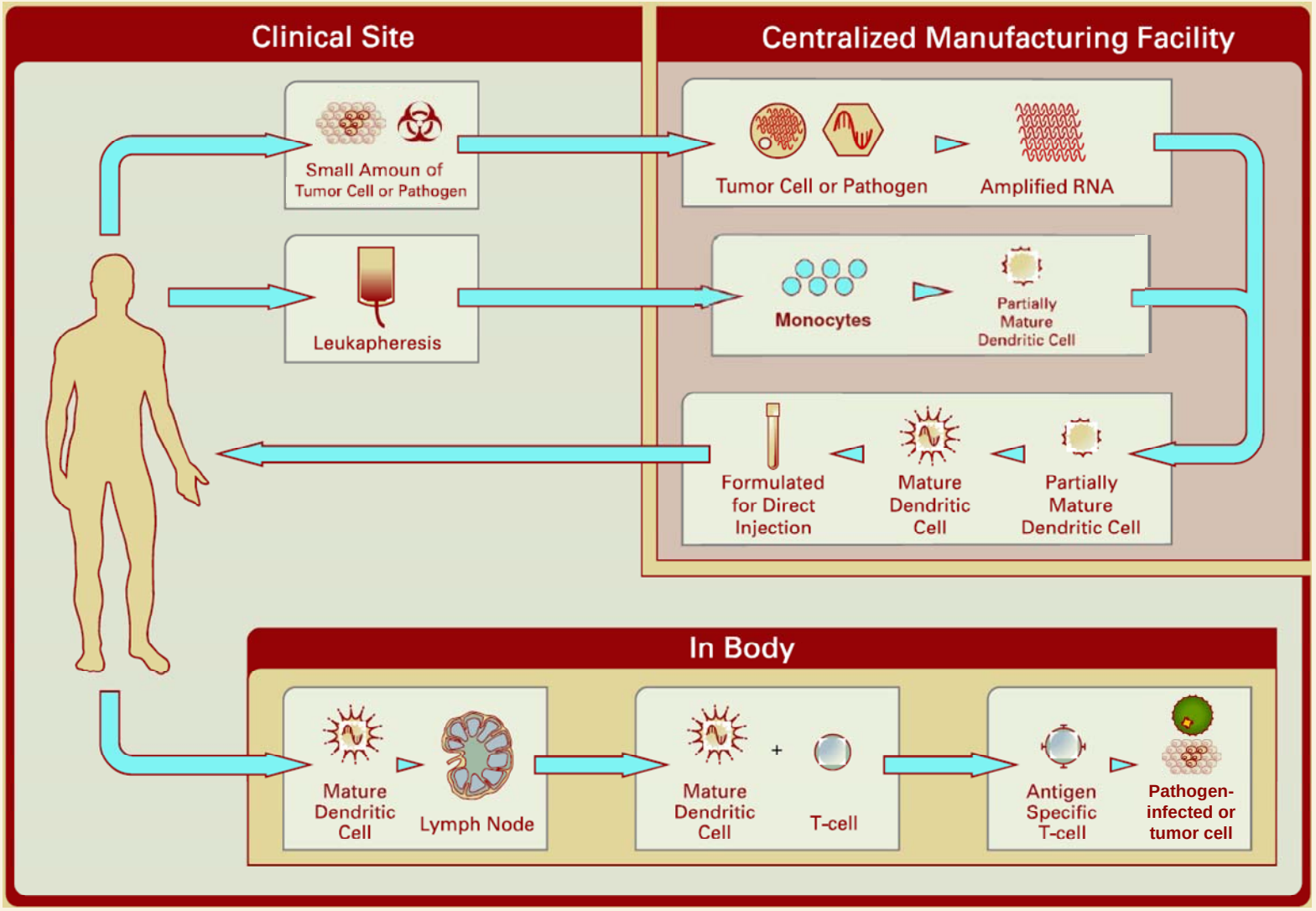
Present Use of DCs in Clinical Studies

- Various strategies of differentiation
- Various loading strategies
  - Passive vs. active
  - Peptides, RNA, DNA constructs
- Various clinical administration strategies
  - Intradermal
  - Intranodal
  - Subcutaneous
  - Intravenous

Argos Autologous RNA-Loaded Dendritic Cell Immunotherapy: Arcelis™

- Powerful Antigen Presenting Platform
  - **Monocyte-derived dendritic cells** (DCs)
- Effective Antigen Amplification Platform
  - **RNA-based**
  - Polyvalent
  - Captures “private mutations’
- Advanced Processes
  - **Centralized manufacturing**
  - Automated, functionally closed
- Ability to induce effective CD8 response without the need to activate CD4+ compartment (HIV)

Arcelis™ Platform Overview



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Arcelis™ Platform in Three Clinical Settings

- Renal Cell Carcinoma (RCC)
  - Single agent
  - Combination with TKI
- Chronic Lymphocytic Leukemia (CLL)
  - Hematologic tumor
- Human Immunodeficiency Virus (HIV)
  - Infectious disease

Issue 1: Non-Clinical Package

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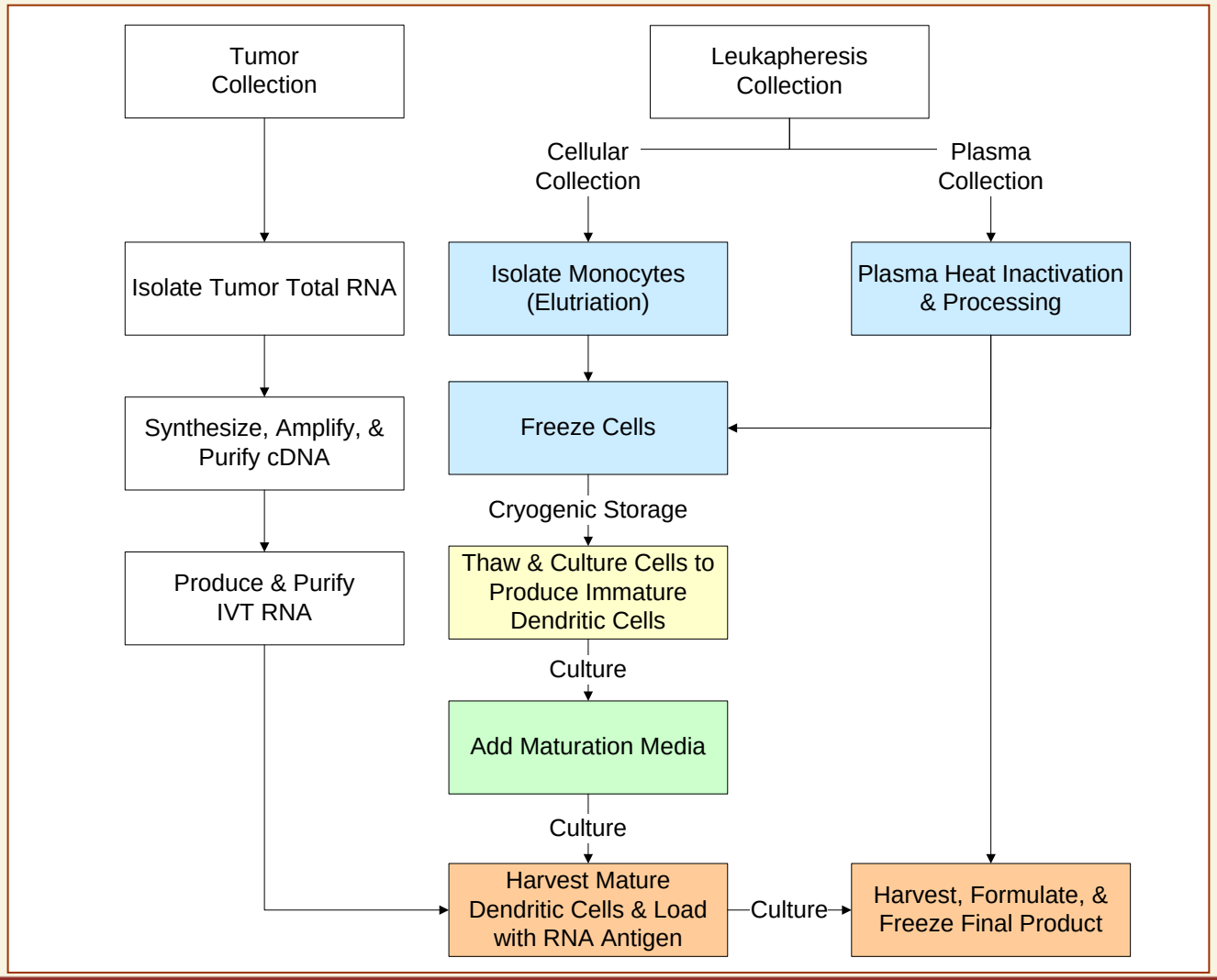
Issue 1: Non-Clinical Package
Chemistry Manufacturing Controls

- Celltherapy not a “well defined drug”
- Product defined through process and controls
- Product Characterization
  - In-process QC
  - Sterility
  - Phenotypic Characterization
  - Viability
  - Stability
  - Release
  - Controlled Storage
  - Controlled Shipment

Issue 1: Non-Clinical Package
Chemistry Manufacturing Controls

- Translate academic bench research into a GMP compliant manufacturing process
  - Academia ➔ Development Stage Manufacturing
  - Local ➔ Central
  - Fresh Leukapheresis ➔ Day old
  - Conventional Cell-culture ➔ Functionally closed
  - Experience/Art ➔ Standardized/Reproducible

Current Processing Overview - Oncology



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Issue 1: Non-Clinical Package Toxicology

- Autologous product
- Conventional test not applicable
- Lack of adequate animal models
- Academic Human Data specific to the product
  - Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res. 2003; 63(9): 2127-33
- Collective Published Evidence in the field
  - The first 1000 dendritic cell vaccinees. Cancer Invest. 2003; 21(6): 873-86

Issue 2: Phase 1 Considerations

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Issue 2: Phase 1 Considerations

- Choice of clinical setting - RCC
  - Tumor type
    - "susceptible to immunotherapy"
    - Only curative treatment: High dose IL-2
  - Extent of tumor
    - Adjuvant vs. MRD vs. bulky
    - Primary removed per standard of care
  - Medical Need and Market Potential
    - 2004: chemo/radio-resistant, just IFN and IL-2
  - Pre-existing evidence
    - Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res. 2003; 63(9): 2127-33
    - Comparison of "academic" product and data with "corporate" data

Issue 2: Phase 1 Considerations

- Endpoints
  - Safety
    - Dose: Conventional dose escalation/MTD not applicable
    - General CTCAE
    - Special considerations re: auto-immunity
      - Lab panel: RF, ANA, etc.
      - Renal function: contra-lateral kidney in place
  - Biologic activity
    - Large volume IM blood draws for ELISpot
    - IM leukapheresis
  - Clinical activity
    - Indicator lesion(s) – RECIST
    - Survival endpoints

A PHASE I/II STUDY IN PATIENTS WITH STAGE IV RENAL CELL CARCINOMA (RCC) VACCINATED WITH AUTOLOGOUS DENDRITIC CELLS (DCS) TRANSFECTED WITH AUTOLOGOUS AMPLIFIED TUMOR-DERIVED mRNA

JJ Knox, DK Ornstein , WK Rathmell, MK Wong, M Jewett, LH Finke, F Miesowicz, CA Nicolette, G Batist

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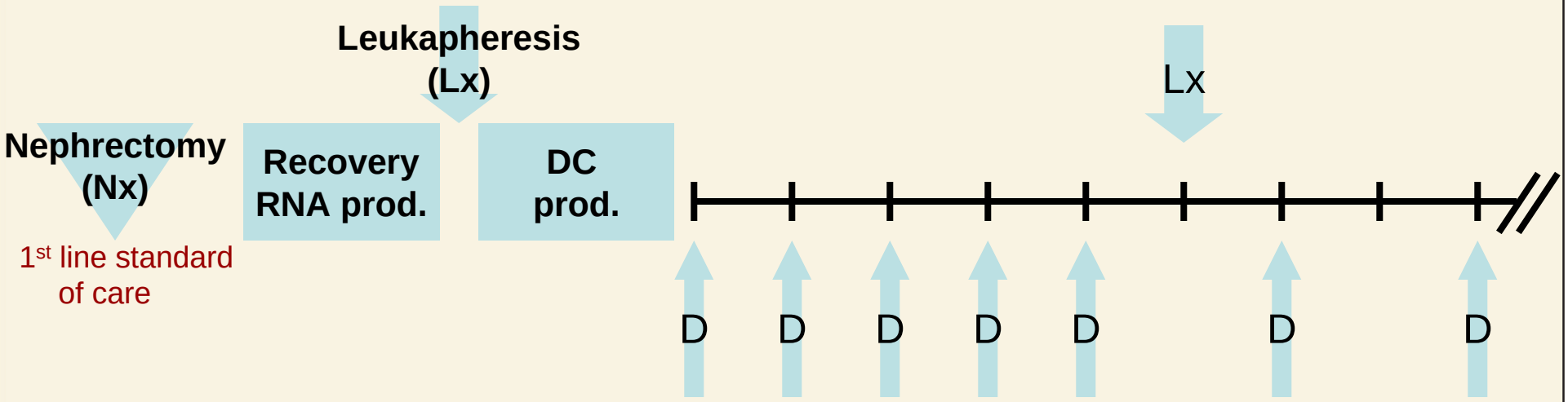
Completed Phase 1/2 RCC Trial - Design



Dosing Regimen:

- 5 x every 2 weeks
- 4 x every 4 weeks
- Every 12 weeks until progression
- Follow up for survival

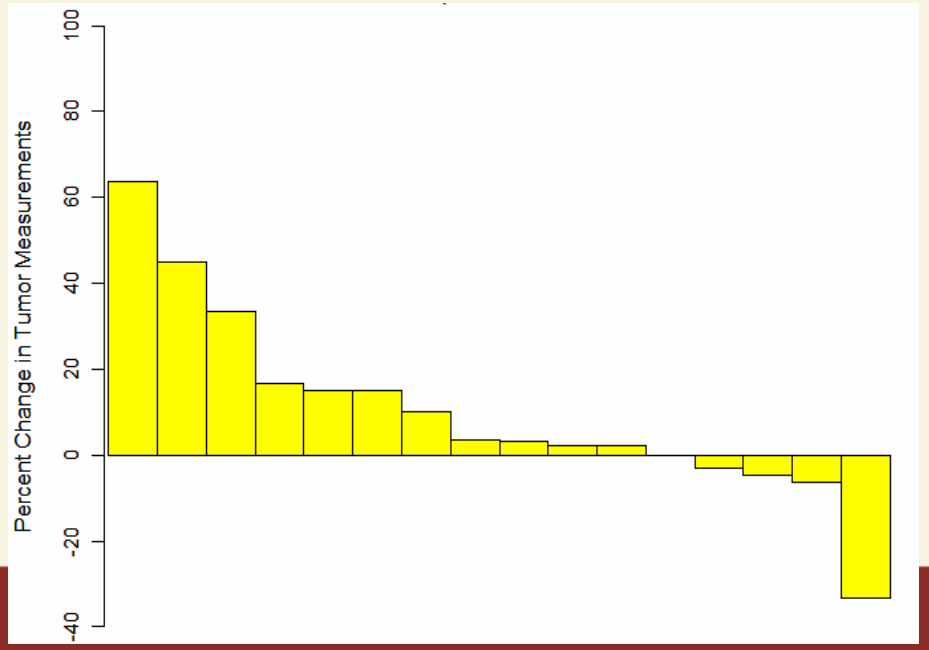
Phase I/II RCC Study - Safety

- No autoimmune AEs, No kidney function impairment
- No drug related SAEs and no drug related Grade III or IV AEs
- 88% of all AEs were Grade I or II
  - 54% of AEs were related to MB-002
  - 95% of MB-002s related AEs were due to injection site reactions

Drug Related Adverse event	N=20
General/administration site (i.e., injection site rxn, axillary pain, fatigue, flu-like illness)	70%
Skin/subcutaneous tissue (i.e., rash, pruritis, urticaria)	30%
Musculoskeletal (i.e., arthralgia, stiffness)	20%
Nervous system (i.e., headache)	10%
Lymph Node pain	5%
Pharyngolaryngeal pain	5%

Phase I/II RCC Study – Clinical Activity

- Clinical Endpoints
  - Predominantly stable disease
  - No confirmed objective response
  - Disease stabilization upon induction treatment in 5 out 6 subjects who experienced progression between Dx and start of treatment



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Phase I/II RCC Study - Activity

- Immune Response (ELISPOT)
  - RCC patients were deficient in T cell IFN-γ and IL-2 production pre-treatment
  - Patients recovered some but not all immune deficiency
  - MB-002 treatment induced an increase in tumor antigen-specific* T cells in 8 of 12 Pts
  - 7 of 12 patients had response to more than one RCC biology relevant antigens post-treatment

RCC Study - Activity

	Arcelis	IFN alone	Nexavar	Sutent
Predominant MSKCC score	0-2	0-2	0-2	0-2
Progression-free survival (months)	6.9	4.1	5.7	11
Median overall survival (months)	**24.7**	**11.1**	**17.8**	**TBD**
Side-effect profile	No serious side effects	Fatigue, Depression	GI, skin toxicities	Hematologic, GI toxicities

Report Card: First Corporate Study

- Signals of clinical activity
  - PD to SD
  - PFS and OS
- Cytokine maturation product has incomplete biologic activity
  - IL-2 but no IFN-γ
- Feasibility
  - Central manufacturing
  - Central immune monitoring

Lessons Learned: First Corporate Study

- RCC induces profound immune suppression
- **Healthy volunteer material, although essential for process development and qualification work has limitations**
- Further translational research needed to tackle RCC impact on immune system
- **Further product optimization needed for full biologic activity in the RCC advanced stage background**

Issue 3: Translational Package

Issue 3: Translational Package

- Multiple procurement protocols –
  Non-Treatment Studies
  - Tissue
  - Blood draws & Leukapheresis
    - RCC: No systemic treatment, TKI
    - HIV: pre-ART and on ART
    - CLL: Leukemia cells vs. healthy monocytes
- PoP studies
  - VHL typing and immune response mapping

Issue 4: Product Optimization

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Arcelis™
Three Generations of Products

1st Generation	2nd Generation	3rd Generation
Academic Product	MB-002	AGS-003
• Total tumor RNA	• **Amplified total tumor mRNA**	• Amplified total tumor mRNA
• Passive transfection	• **Active electroporation**	• Active electroporation
	• **Cytokine maturation**	• **PME CD40L maturation**
		• **Elutra FT improved monocytes**

Immature DCs — **Mature DCs**

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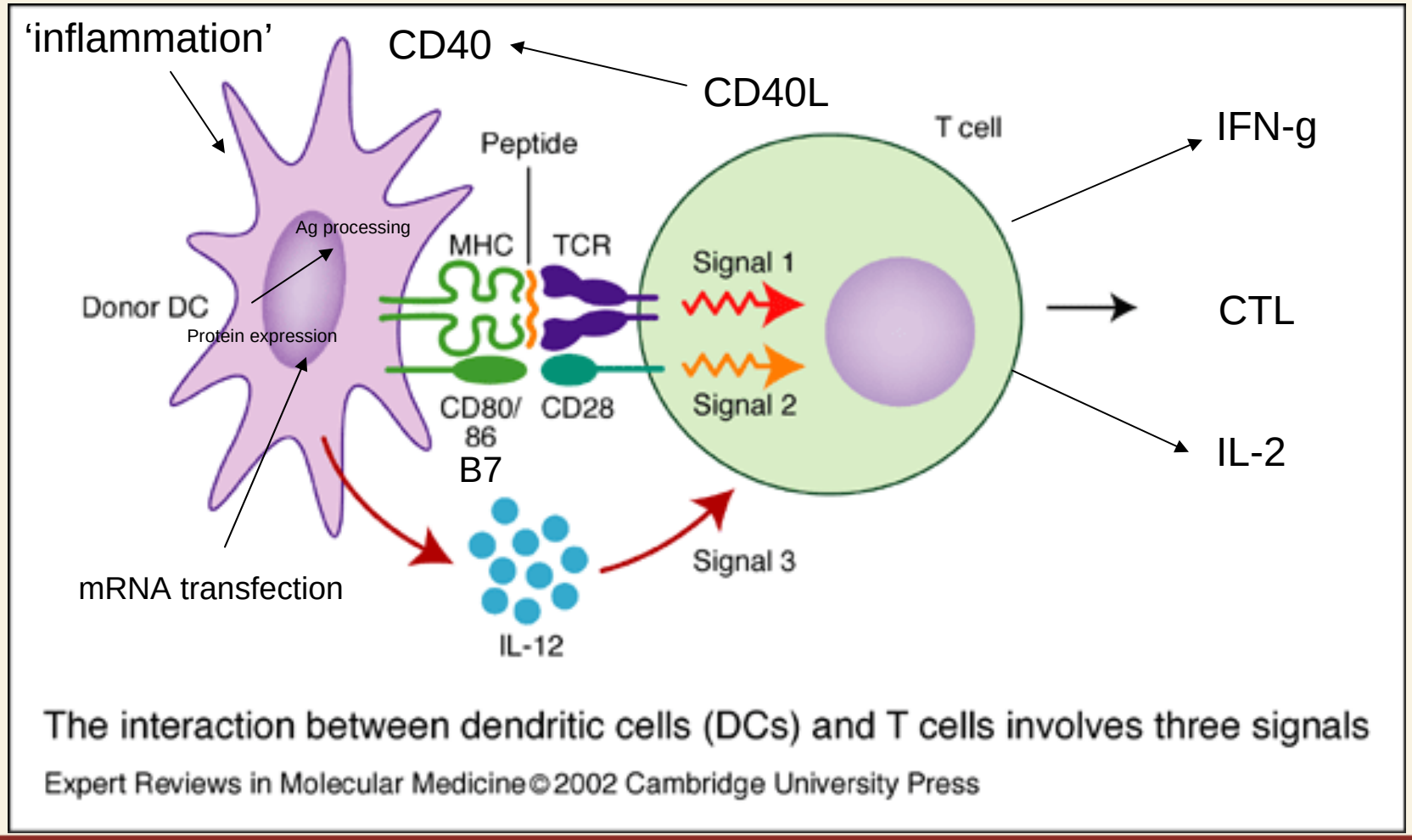
Dendritic Cell – T-cell:

Interaction between innate and adaptive immunity facilitated by IL-12



The interaction between dendritic cells (DCs) and T cells involves three signals

Issue 4: Product Optimization

- Rational
  - Immune monitoring told us that cytokine maturation process does not yield the full biologic activity when applied to RCC subjects
  - Safety and clinical data quite encouraging
- Action taken
  - Take CD40L co-stimulation into the manufacturing process and optimize maturation and loading protocol
  - Cut turn around time
  - Move to functionally closed systems
  - Start robotized manufacturing program
- Implementation
  - Tech Transfer and qualification
  - Regulatory submission

Issue 5: Suitable Study Designs

Issue 5: Suitable Study Designs

1. Confirmation of biologic rational
   - When going back to the clinic, first confirm that with the PME-CD40L product shows desired biologic activity: IL-2 & IFN-γ by ELISpot
   - Confirm similar safety profile
   - Build on legacy data from previous studies
2. Conserve resources in a VC funded start-up environment
   a. Start with a small PoP sample with a strict go/no-go criterion for in vivo biologic activity
   b. Adapt to single stage or two stage phase 2 design
3. Collect information on accepted oncology clinical endpoints
   - RECIST endpoints
   - PFS, OS

AGS-003-004

A PHASE I/II STUDY TESTING THE BIOLOGIC ACTIVITY AND SAFETY OF AGS-003 AS AN IMMUNOTHERAPEUTIC IN SUBJECTS WITH NEWLY DIAGNOSED ADVANCED STAGE RENAL CELL CARCINOMA (RCC)

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AGS-003-004
Study Overview

- Step I:
  - Objective:
    > 5/8 subjects with polyvalent IL-2 and IFN-γ immune monitoring
    AND
    safety similar to first study
- Step II:
  - Two stage design
    - 18 + 17
  - Objective:
    - 3 PR / 18
    - 5 PR / 35
    - Monitor pertinent accepted clinical endpoints
    - Continue thorough immune monitoring

Immune Monitoring: First data with AGS-003

AGS-003

SUMMARY OF IMMUNE MONITORING DATA								
	Pre-Vaccination				Post-Vaccination			
	Screening Visit		At 1st Vaccine		After 3rd Vaccine		After 5th Vaccine	
Patient ID	IFN-γ	IL-2	IFN-γ	IL-2	IFN-γ	IL-2	IFN-γ	IL-2
001	F	-	F,G	G,S,F	F	G,F,S	F,G	-
002	-	-	-	S	F,S	S	ND	ND
003	-	S	-	-	F,S	S,F	-	-
004	-	-	-	F	F,S	S,F	S,F	-
005	-	-	ND	ND	ND	ND	S,G,T,F	S,G,F

MB-002

	Pre-Vaccination				Post-Vaccination			
	Screening Visit		At 1st Vaccine		After 3rd Vaccine		After 5th Vaccine	
Patient ID	IFN-γ	IL-2	IFN-γ	IL-2	IFN-γ	IL-2	IFN-γ	IL-2
AA-AAAA	-	-	-	-	-	S,G,F	-	S,F
AA-AAAF	-	-	-	-	-	S,G,F	-	S,G,F
AA-AAAI	-	-	-	-	-	-	-	-
AA-AAAL	-	-	-	-	-	R, G	-	R,G,F
AA-AAAK	-	-	-	-	-	-	-	-
AA-AAAH	-	-	G	G	G	S, G	G	S,G,F
AA-AAAB	-	-	-	-	-	-	-	-
AA-AAAM	-	-	-	-	-	S,G,T,F	-	G,T,F
AA-AAAP	-	-	-	-	-	-	-	-
AA-AAAS	-	-	-	-	-	-	-	-
AA-AAAU	-	ND	-	ND	-	ND	-	ND
AA-AAAV	-	-	-	-	-	-	-	-

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AGS-003-004
Study Overview (Step II)

- Open-label, multi-center, two-stage, Phase I/II single agent clinical study
- Subjects with newly diagnosed metastatic clear cell RCC
- Primary endpoints:
  - Clinical response: PR and CR (RECIST)
  - Immune response
- Secondary endpoints:
  - Overall and progression free survival (RECIST)
  - AGS-003 production feasibility
  - Safety
  - Exploratory assays of T cell functionality and AGS-003 immunogenicity

Issue 6: Combination Therapy

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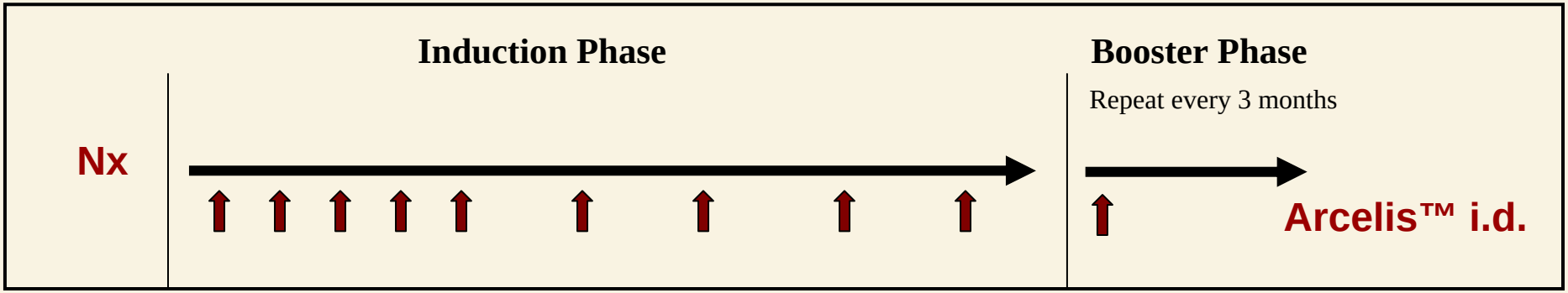
Arcelis TKI Combination - Rationale

- SORAFENIB BUT NOT SUNITINIB INHIBITS HUMAN T-CELL FUNCTION (iSBTc Oct 2007)
- Supported by four independent groups
  - Immatics (Germany)
  - Cleveland Clinic
  - Dana Farber
  - Argos (leukapheresis material from TKI treated patients and *in vitro* studies)
- Arcelis / Sunitinib combination
  - First protocol to clear FDA and Health Canada

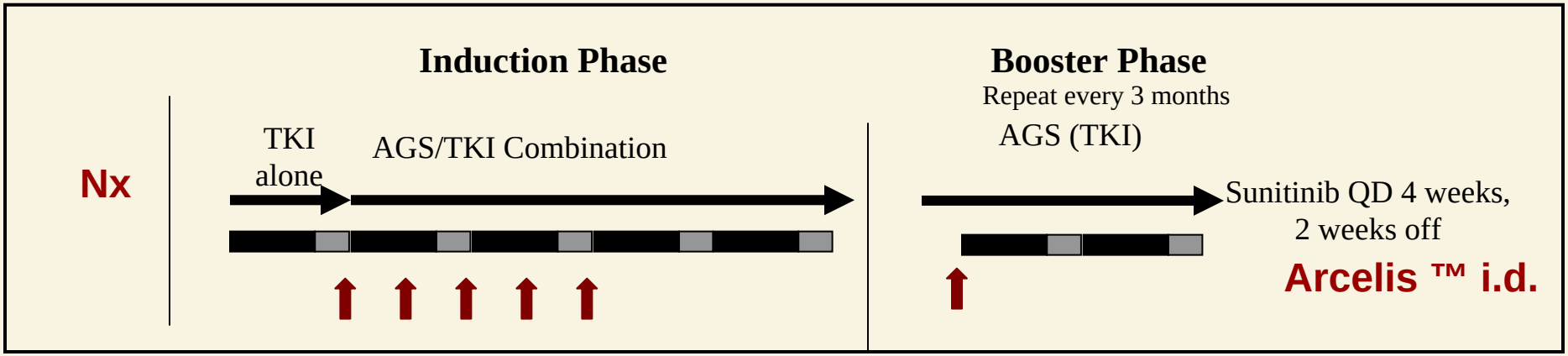
Dual Track Ph II Clinical Study Program:

- Newly diagnosed advanced stage RCC -

Single Agent first line (2 Stage "Simon Design")



Combination with Sunitinib first line (Singe stage design)



Nx - nephrectomy ⬆ - Arcelis™ Dosing

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AGS-003-006

A Phase II Study Testing the Safety and Activity of AGS-003 as an Immunotherapeutic in Subjects with Newly Diagnosed Advanced Stage Renal Cell Carcinoma in Combination with Sunitinib

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Arcelis TKI Combination - Design

- Multi-center single stage Phase II Study
- Centers in US and Canada
  - Plenty of very supportive interaction with FDA and Health Canada leading up to the IND and CTA submissions
- Newly diagnosed RCC or metachronous metastatic disease
  - Leukapheresis prior or after surgery
  - RNA from nephrectomy or metastectomy specimen
  - Cycled into Sunitinib (at reconstitution and prior to leuk drop)
- Requires a DMC

Issue 7: cGMP Manufacturing

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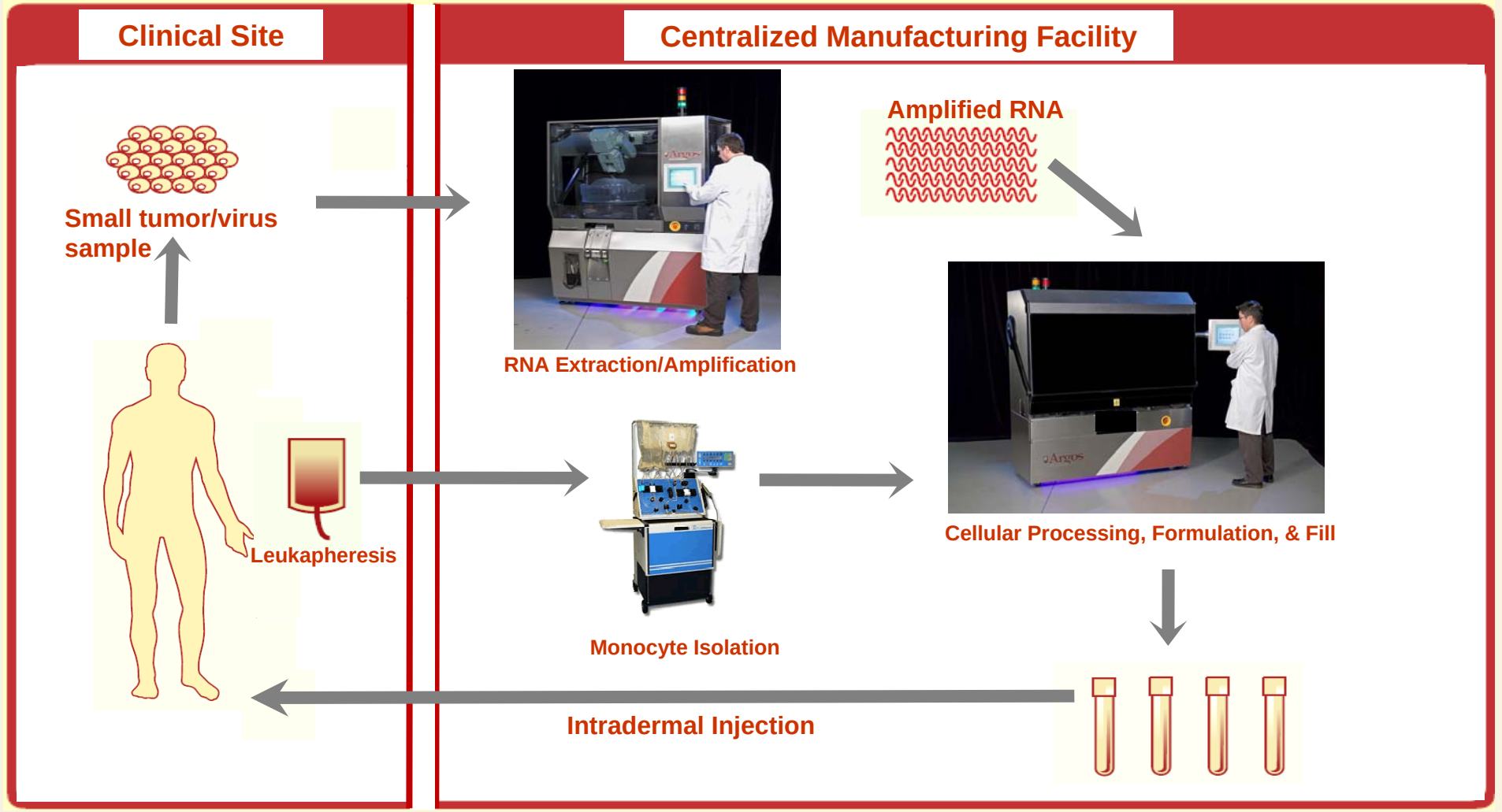
Milestones in Process Development

1st Generation Academic Product	2nd Generation MB-002	3rd Generation AGS-003	Robotized Automation
• fresh monocytes • open cell culture • little GC	• day old monocytes • flask culture • establish GMP quality systems • 12 weeks turn around	• PME CD40L process • bag culture • functionally closed systems	• more functionally closed systems • modular, scalable manufacturing units

• establish clinical development & regulatory departments
• SOPs, practices, standards

Immature DCs — **Mature DCs**

Automated Manufacturing Process



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RNA Automated Processing

Conclusions

Case Studies: Lessons and Issues
Autologous RNA loaded DCs – Arcelis™

- Key Strategic Decisions
  - Are cooked fresh every morning
  - Stick to your biologic hypothesis
  - Ask every day: “what made us put this into the clinic?”
- Impact of Regulatory Interactions
  - Crucial and enabling
- Financial Considerations: Projected Costs vs. Reality
  - Cost: Follow press releases of companies in this space

  BUT
  - **Personalized celltherapy can be done now!**
- Lessons Learned
  - Immune monitoring
  - Limitations of healthy volunteer material
  - Single agent vs. combination in present day oncology

Acknowledgments

- Clinical Investigators
- Healthy volunteers and patients on the non-treatment protocols
  - Samples, leukaphereses
- Patients and their families on the clinical studies
- Scientific founders and investors
- iSBTc allowing us to present