Dendritic cell vaccines:
Current research progress, challenges and opportunities

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Outline

- Role of Dendritic Cells in Anti-Tumor Immunity
- Classical DC Vaccine Approach
- New Generation DC Vaccines
- Future Perspectives & Remaining Challenges

Introduction:
Cancer Immunotherapy Landscape

Approach	Limitation
ICBs(Immune Checkpoint Blockades)	• NO response in cold tumors • Require pre-existing immunity • Immune-related adverse events
ACTs(Adoptive Cell Therapies)	• Limited to surface antigens • "On-target off-tumor" toxicity risk • Antigen escape

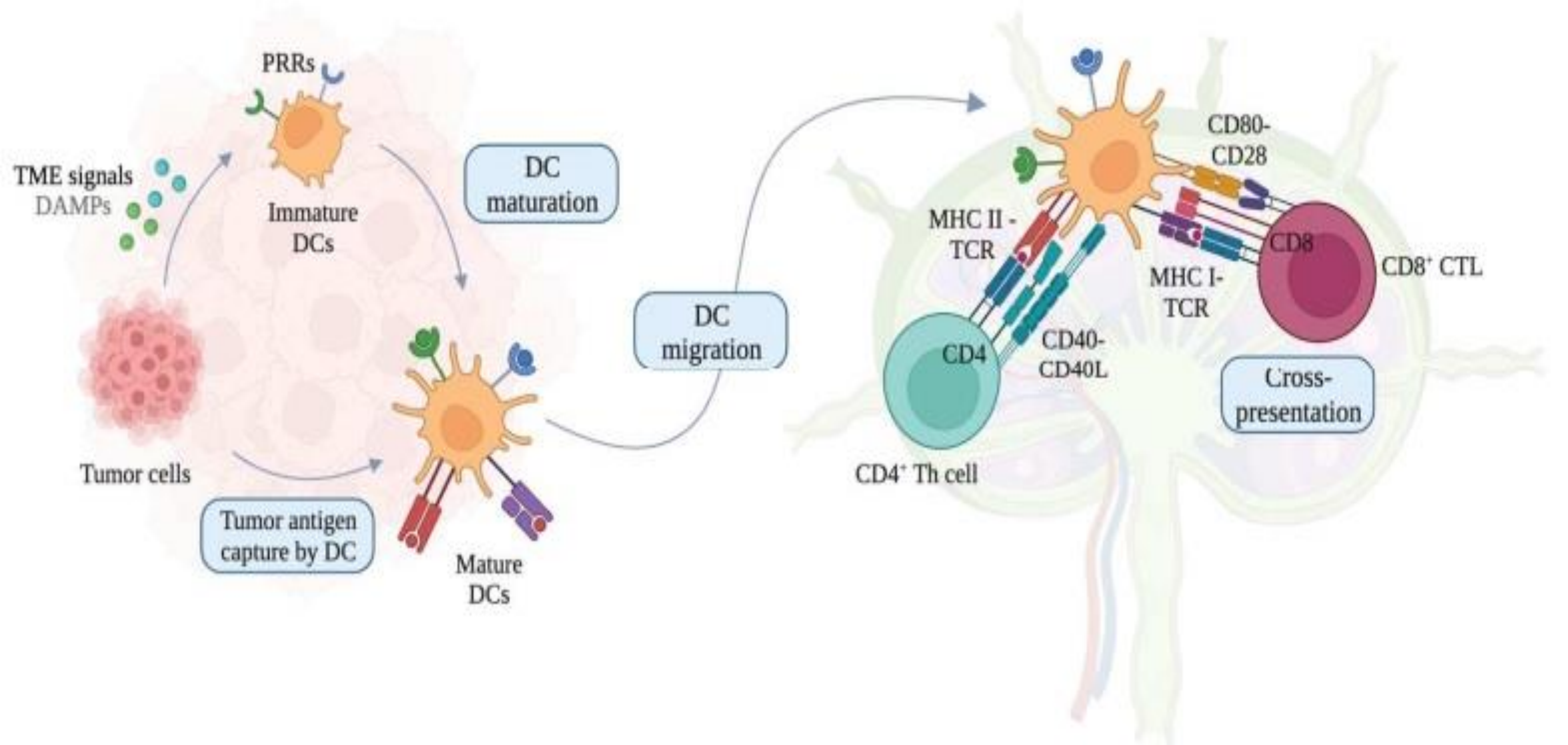
Why Cancer Vaccines?
• Target intracellular antigens • Prime naïve tumor-reactive T cells • Generate durable immunological memory • Can be part of multimodal regimens

Role of Dendritic Cells in Anti-Tumor Immunity

- Dendritic Cells(DCs): The Most Potent Antigen-Presentation Cells
- Main DC Subsets:
  - cDC1
  - cDC2
  - pDCs
  - MoDCs(Monocyte-derived)

1. DAMPs from tumors activate DCs via PRRs
2. DCs capture antigens and migrate to lymph nodes
3. Present antigens on MHC molecules
4. Prime naïve T cells into CD4+ Th and CD8+ CTLs

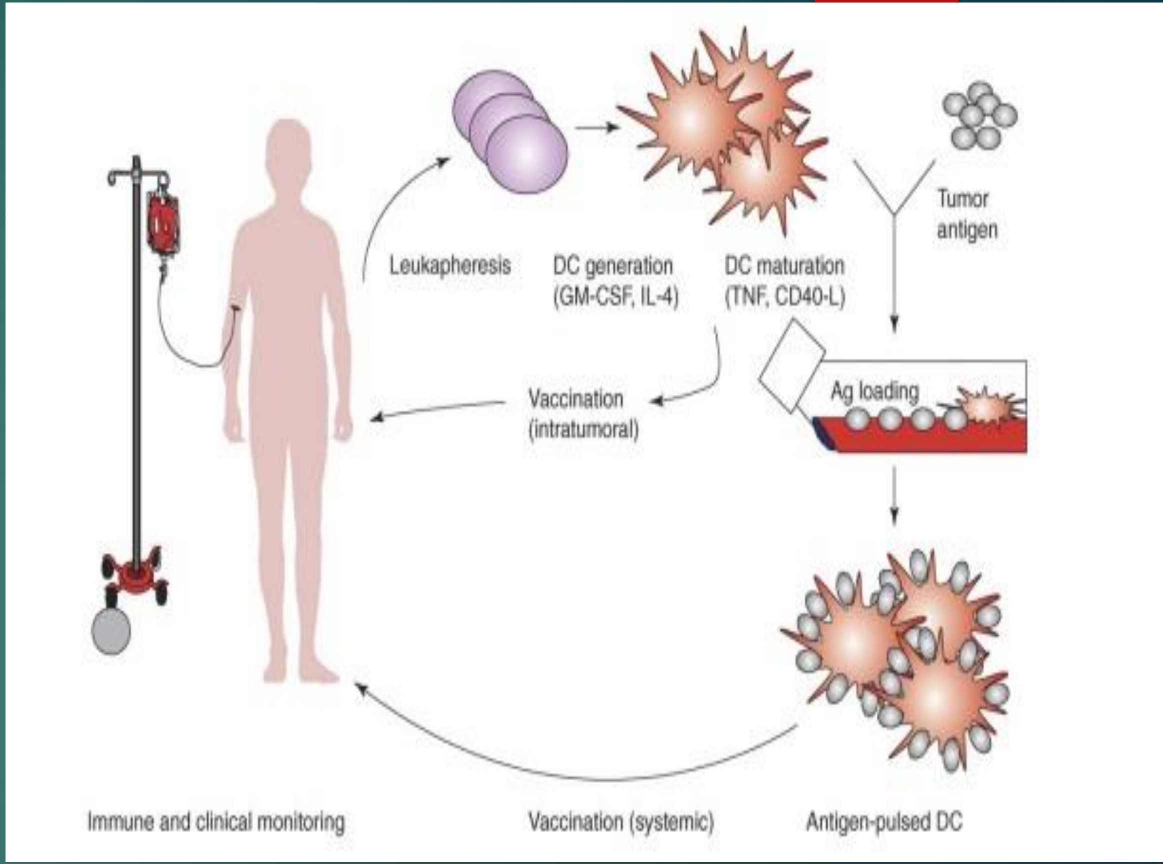
Role of Dendritic Cells in Anti-Tumor Immunity



Classical DC Vaccine Approach

Two Main Strategies:

- **Ex Vivo Differentiation(97% of clinical tials):**
  - Day 0: Leukapheresis → CD14+ selection
  - Day 6: Differentiation with GM-CSF + IL-4
  - Day 7: Maturation cocktail (TNF-α, IL-1β, IL-6, PGE2)
    - └── Simultaneous antigen pulsing
  - Day 9: Reinfusion into patient
  - Limitations:
    - ❌ Expensive and labor-intensive
    - ❌ Requires leukapheresis
    - ❌ Poor migration to lymph nodes
    - ❌ Functionally different from endogenous DCs



- **In Vivo DC Targeting:**
  - Antigen coupled to mAbs targeting DC receptors (Clec9A, CD40, DEC-205)
  - Drawbacks: Requires specific receptor expression, needs co-administered adjuvants

Provenge(Sipuleucel-T)

- First FDA-approved therapeutic cancer vaccine
- For metastatic castration-resistant prostate cancer
- Phase III trial (NCT00065442) showed improved survival
- Combination with ICBs and IL-7 shows promise

Limitations of Classical DC Vaccines

- **Clinical Efficacy Issues:**
  - Only 5-15% patients show objective immune response
  - Poor migration to tumor-draining lymph nodes (TDLNs)

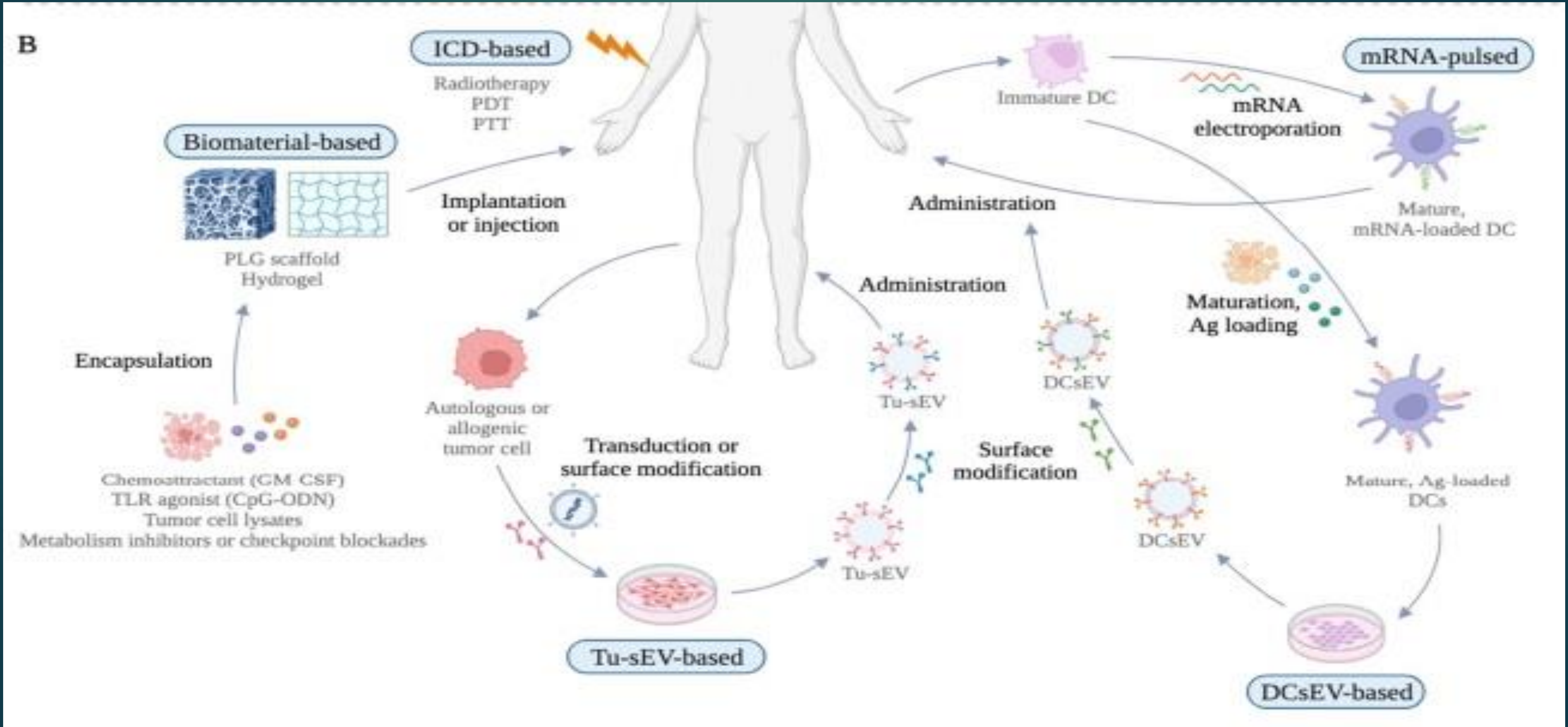
- **Technical Limitations:**
  - MoDCs functionally dissimilar to endogenous DCs
  - Extensive in vitro culture alters functionality
  - Expensive and labor-intensive production
  - No standardized preparation protocol
  - Short half-life of pMHC complexes

Limitations of Classical DC Vaccines

- **Immunosuppressive TME Factors:**

Factor	Effect
IDO	Suppresses Th1 and CTL activity
TGF-β	Impairs DC function
VEGF	Inhibits DC maturation
Tregs	Suppress immune response
MDSCs	Inhibit T cell activation
Checkpoints (CTLA-4, PD-1)	Immune evasion

New Generation DC Vaccines



Biomaterial-Based DC Vaccines

Implantable or injectable scaffolds that recruit and activate endogenous DCs in situ

PLG Scaffold Vaccines:

- Material: Poly(lactide-co-glycolide) - FDA-approved, biocompatible, biodegradable
- Components encapsulated:
  - Chemoattractant: GM-CSF (sustained release over 15 days)
  - Adjuvant: CpG-ODN (TLR9 agonist)
  - Antigens: Tumor lysates
- Key Findings:
  - Recruits heterogeneous DC subsets (pDCs and CD8+ cDCs)
  - Complete tumor regression in ~47% of melanoma-bearing mice (two vaccinations)
  - Increased IL-12 production (Th1-promoting)
  - CTLs outnumber Tregs at vaccine site
  - WDVAX: Human version in Phase I trial for stage IV melanoma (NCT01753089)
  - Combination with anti-CTLA-4 enhances efficacy

Biomaterial-Based DC Vaccines

Injectable Hydrogels (Alginate):

- Advantages: No surgery required, sustained molecule release
- Cryogelination: Enhances mechanical stability and pore connectivity
- Combination strategies:
  - Metabolism inhibitors (epacadostat - IDO inhibitor)
  - Checkpoint blockades
  - Chemotherapeutics (DOX)
  - Kynureninase (KYNase) for Kyn depletion

Results:

- 12-fold increase in intratumoral cDCs, Increased CD86 maturation marker,
- Higher CTLs/Treg ratio, <u>Abscopal</u> effect in untreated tumors

Immunogenic Cell Death (ICD)-Inducing DC Vaccines

Convert "cold" tumors to "hot" tumors by inducing immunogenic cell death

- **ICD Triggers:**

Therapy	Mechanism
Radiotherapy	DNA damage, abscopal effect
Chemotherapy	Stress-induced cell death
Photodynamic Therapy (PDT)	ROS generation
Photothermal Therapy (PTT)	Heat-induced ablation

- **Key DAMPs Released During ICD:**

DAMP	Function
Calreticulin (CRT)	"Eat-me" signal, promotes phagocytosis
ATP	"Find-me" signal, recruits DCs
HMGB1	Activates DCs, enhances cross-presentation
HSP70	Increases tumor cell uptake, DC maturation

Radiotherapy-Based In Situ Vaccines

Local Radiotherapy +TLR agonists(poly-ICLC, CpG-ODN)+Flt3L(adjuvant)

- Results:
  - Increased intratumoral CD8+ T cells
  - Improved systemic tumor remission (40% → 80%)
  - Delayed metastases
  - Synergizes with PD-1/PD-L1 blockade

- Clinical trials:
  - NCT01976585 (Lymphoma)
  - NCT03789097 (Breast, Head & Neck)
  - NCT00185965 (Various cancers)

PDT and PTT in DC Vaccines

Photodynamic Therapy (PDT):

- Photosense (PS) + light → ROS
- DCs loaded with PDT-treated glioma cells

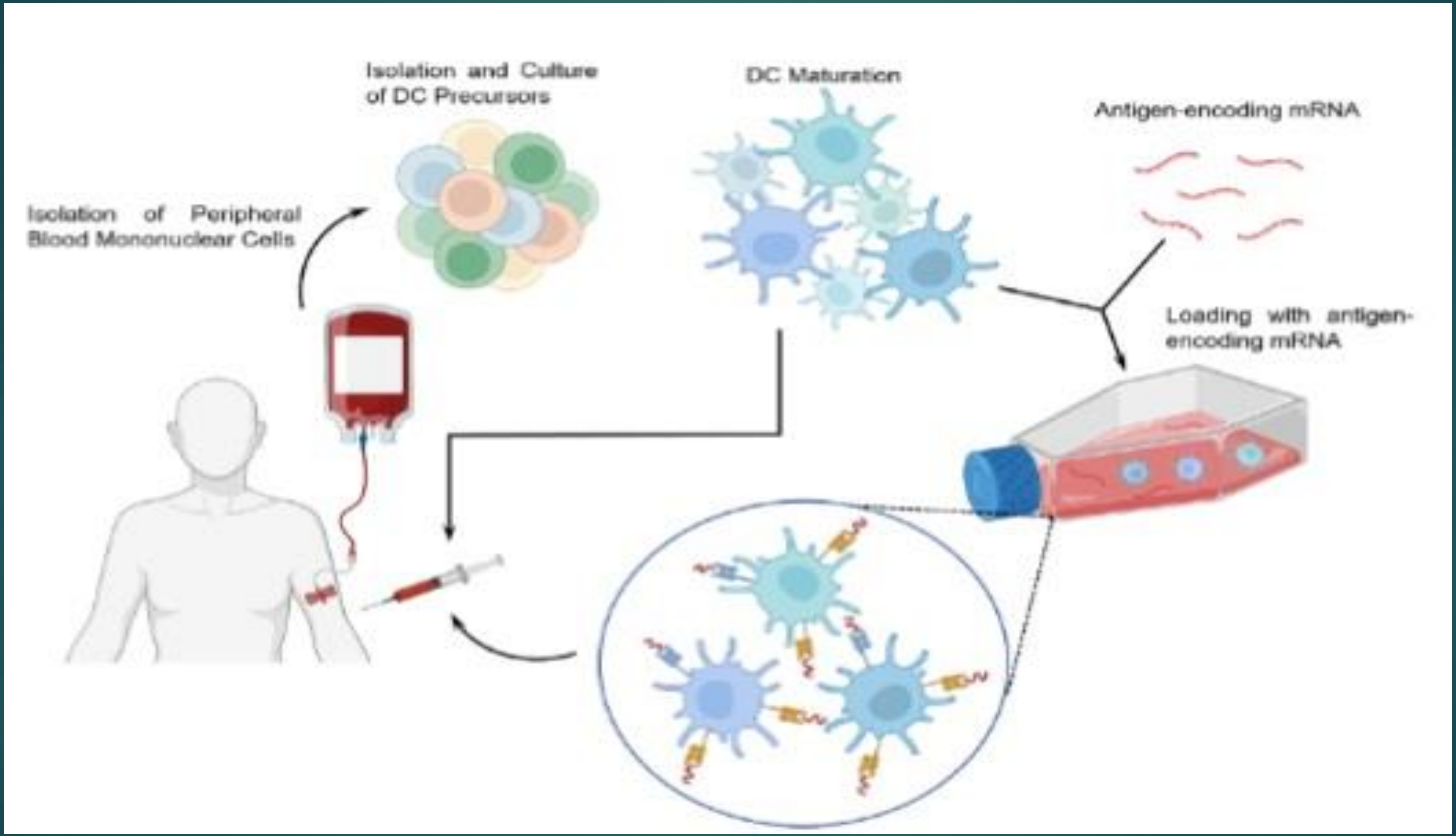
Chimeric polymersome (CCPS) +DOX(chemotherapy) + PS:

- 19-fold increase in DC maturation
- Elevated IL-6, IL-12, TNF-α
- Significant abscopal effect

Photothermal Therapy (PTT):

- PLG-ICG-R837 + NIR laser
- Complete inhibition of secondary tumors (4T1 breast cancer and CT26 colorectal cancer)
- Long-term anti-tumor immunity

mRNA-Pulsed DC Vaccines



mRNA-Pulsed DC Vaccines

- **Advantages of mRNA:**
  - Stimulates TLR3, TLR7, TLR8 (intrinsic adjuvanticity)
  - No genomic integration
  - Large-scale production
  - No splicing uncertainty
  - Can be engineered for stability and translation
- **mRNA Sources:**

Source	Advantages	Disadvantages
Whole tumor-derived mRNA	Complete epitope repertoire	Requires large tumor sample, contains self-antigens
In vitro transcribed mRNA	Controlled, reproducible	Lower T cell responses

mRNA-Pulsed DC Vaccines

Enhancing CD4+ T Cell Responses:

- **Problem**: mRNA-encoded antigens presented on MHC I only (CD8+ stimulation)
- **Solution**: Fusion to lysosomal targeting signals
  - LAMP-1 (lysosome-associated membrane protein-1)
  - MITD (MHC I trafficking signal)
- Results: Both CD4+ and CD8+ T cell responses
- Clinical trials: NCT00626483, NCT00639639, NCT02366728 (glioblastoma)

mRNA-Pulsed DC Vaccines

- **Co-Transfection Strategies:**

Molecule	Function
CD83, OX40L, 4-1BBL, CD40L, GITRL	Enhanced co-stimulation
TriMix (CD70 + CD40L + caTLR4)	Reprograms Tregs to Th1-like cells
IL-12, IL-15	Enhanced Th1 differentiation
Bcl-2	Pro-survival, enhances DC viability
Anti-CTLA-4, anti-PD-1 mAbs	Checkpoint blockade

- **Rocapuldencel-T:**
  - Most clinically advanced mRNA-pulsed DC vaccine
  - Autologous tumor mRNA + CD40L mRNA
  - Failed to improve overall survival in mRCC (Phase III terminated)

mRNA-Pulsed DC Vaccines

- **Administration Routes:**

Route	Advantages
Intratumoral	Exploits autologous antigen repertoire
Intranodal	Direct T cell activation site
Intradermal	Rich in APCs
Intravenous (with lipoplex)	Protects mRNA, targets lymph node DCs

- **mRNA-lipoplex:**
  - Tunable surface charge
  - Targets lymph node DCs
  - Trials: NCT02410733, NCT02316457

DC-Derived Small Extracellular Vesicle (DCsEV) Vaccines

- **Advantages of Cell-Free Approach:**
  - Resistant to immunosuppression
  - 10-100× more pMHC II than DCs
  - Frozen storage possible
  - No risk of in vivo replication
  - Highly biocompatible

- **DCsEV Characteristics:**
  - Carry pMHC I, pMHC II, CD80/86, ICAMs
  - Transfer functional pMHC to recipient DCs

DC-Derived Small Extracellular Vesicle (DCsEV) Vaccines

- **Importance of Donor DC Maturation Status:**

Donor DC Status	DCsEV Effect
Immature	T cell tolerance, Treg proliferation
Mature (IFN-γ stimulated)	Enhanced T cell responses, Th1 polarization

- **Generations of DCsEV Vaccines:**

Generation	Features	Limitations/Advantages
First	Peptide-loaded, autologous MoDCs	Limited efficacy, Treg elevation
Second	IFN-γ-matured MoDCs	Still insufficient antigen presentation
Third	Engineered/nanotechnology-modified	Enhanced targeting and immunogenicity

Engineered DCsEVs

"Designer" Vaccine for HCC:

- P47 targeting peptide
- AFP212-A2 antigenic epitope
- N1ND immunoadjuvant (HMGN1 domain)
- **Results**: Tumor-targeted DC recruitment, Increased IFN -γ+ CD8+ T cells, Decreased IL-10/TGF-β

CTLA-4 mAb-Modified DCsEVs:

- Anti-CTLA-4 anchored to OVA-pulsed DCsEVs
- **Results:** Stronger T cell activation, Rapid TDLN migration, Increased CTLs/Treg ratio,Enhanced TEM generation

ASPIRE (Anti-PD-1 DCsEVs):

- Engineered DC2.4 cells with anti-PD-1
- Adenovirus transduction of melanoma TSAs
- **Results:** Complete tumor rejection in B16-F10 melanoma, Direct pMHC I transfer to endogenous DCs, Fewer PD-1+ dysfunctional CTLs

Tumor-Derived sEV (Tu-sEV) Vaccines

Vesicles from Tumor Cells

Advantages:

- Rich source of tumor antigens
- Express MHC, LAMP-1, CD9, CD54 (facilitate DC uptake)
- Easily isolated from patient fluids (non-invasive)
- More immunogenic than tumor lysates

The Dual Nature of Tu-sEVs:

Immunostimulatory	Immunosuppressive
Carry tumor antigens	Induce inhibitory cytokines
Activate DCs	Decrease co-stimulatory molecules
Stimulate CTL responses	Increase STAT3 expression
Prevent metastases	Impair DC maturation
	Expand Tregs

Tu-sEV Engineering Strategies

Genetic Modification of Tumor Cells:

Modification	Result
MUC1	↑ Tumor inhibition, ↑ IFN-γ
IFN-γ	↑ T CD4+, T CD8+ ↓ Treg,PD-L1,IDO
IRF-1	↑MHC I and IL-15Rα, ↑ TILs

MHC II Enrichment:

- CIITA gene transduction
- Results: Greater DC maturation (higher MHC II, CD86, CCR7, IL-12), 20% increased survival at 60 days, Enhanced IFN-γ levels

Adjuvant Co-Delivery Systems:

- CpG + poly(I:C) loading
- Results:Th1-biased immunity, memory T cell responses

Surface Modification:

- N1ND painting via vesicular anchor peptide
- Results:: Activated DCs, Increased TEM generation, Tumor suppression

Comparative Summary Table

Vaccine Type	Advantages	Limitations	Clinical Status
Classical MoDC	Proven safety, Provenge	Suppressive TME, costly	FDA-approved
Biomaterial-based	Spatiotemporal control, recruits endogenous DCs	Requires implantation, multiple doses	Phase I
ICD-inducing	Converts cold to hot tumors, abscopal effect	Requires combination	Phase I/II
mRNA-pulsed	No HLA restriction, intrinsic adjuvanticity	Rocapulencel-T failed	Phase I/II
DCsEV-based	Cell-free, TME-resistant, 10-100× pMHC II, engineerable	Depends on donor DC maturation	Phase II
Tu-sEV-based	Abundant antigens, easy isolation, engineerable	Potential immunosuppressive effects	Preclinical

Conclusions

Key Findings:

- Classical DC vaccines have limited efficacy due to TME and technical challenges
- Biomaterial scaffolds enable in situ DC recruitment and activation
- ICD-inducing therapies convert cold tumors to hot tumors and generate abscopal effects
- mRNA technology offers flexibility and combinatorial potential
- sEV-based vaccines provide cell-free alternatives with unique advantages

Conclusions

Emerging Opportunities:

- Multimodal approaches
- Biomimetic nanoparticles
- Personalized mutanome mapping

Remaining Challenges:

- Optimal DC subset selection
- Protocol standardization
- Understanding sEV biogenesis and biodistribution
- Optimizing administration routes

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Thanks for your attention