Adult stem cells as a therapeutic tool to treat inflammatory diseases

TiGenix
Living Medicines

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The newly created EU Cell Therapy leader

- Result of the combination of **TiGenix and Cellerix**, effective May 2011
- Unique combination of **top line** and promising **development pipeline**
- Two **commercial** products on the market in Europe:

  CHONDROCELECT autologous cell-based product for cartilage repair

  ChondroMimetic™ resorbable implant for small (osteo)chondral defects
- Strong development **pipeline**: programs in Phase III, Phase Ib/IIa and Phase I, based on p**roprietary validated stem cell platform**
- Initial focus on **damaged and arthritic joints**; expansion potential into other **autoimmune and inflammatory diseases**
- Operations supported by dedicated **commercial and manufacturing** infrastructure
- **Solid financial position** to support successful market roll-out of first two products and bring follow-on products through the clinic

Stem cell: what's in a name

- Stem cells
  - Growing a new living organism (development)
  - Keeping a living organism "in good shape" (renewal and maintenance)

- Stem cell properties (NIH)
  - Capable of dividing and renewing themselves for long periods;
  - Unspecialized;
  - Can give rise to specialized cell types.

- Stem cell types
  - Embryonic stem cells (pluripotent)
  - Fetal sten cells (pluri – multipotent)
  - Placental and umbilical cord stem cells (multipotent)
  - **Adult stem cells (multipotent)**
  - Induced stem cells (iPS) (pluripotent)

Adult stem cells

- Present in most adult tissues
- Main role of adult stem cells: tissue renewal and general tissue homeostasis
- Mesenchymal stem cells are non-blood adult stem cells present in a large range of (mesenchymal) tissues. They are often also termed mesenchymal stromal cells
- Common sources of MSC
  - Bone Marrow
  - Adipose tissue
  - Muscle
  - Synovial
  - Dental Pulp
  - ...

Our choice: Adipose stem cells

ASCs

- ✓ **Adult stem cells: No ethical debate** or scientific challenge
- ✓ **Safety**: No tumorigenic behavior after long term ex vivo culture
- ✓ **Expendable** and **easily accessible** though liposuction
- ✓ 100 to 1000 times **higher yield** than bone marrow

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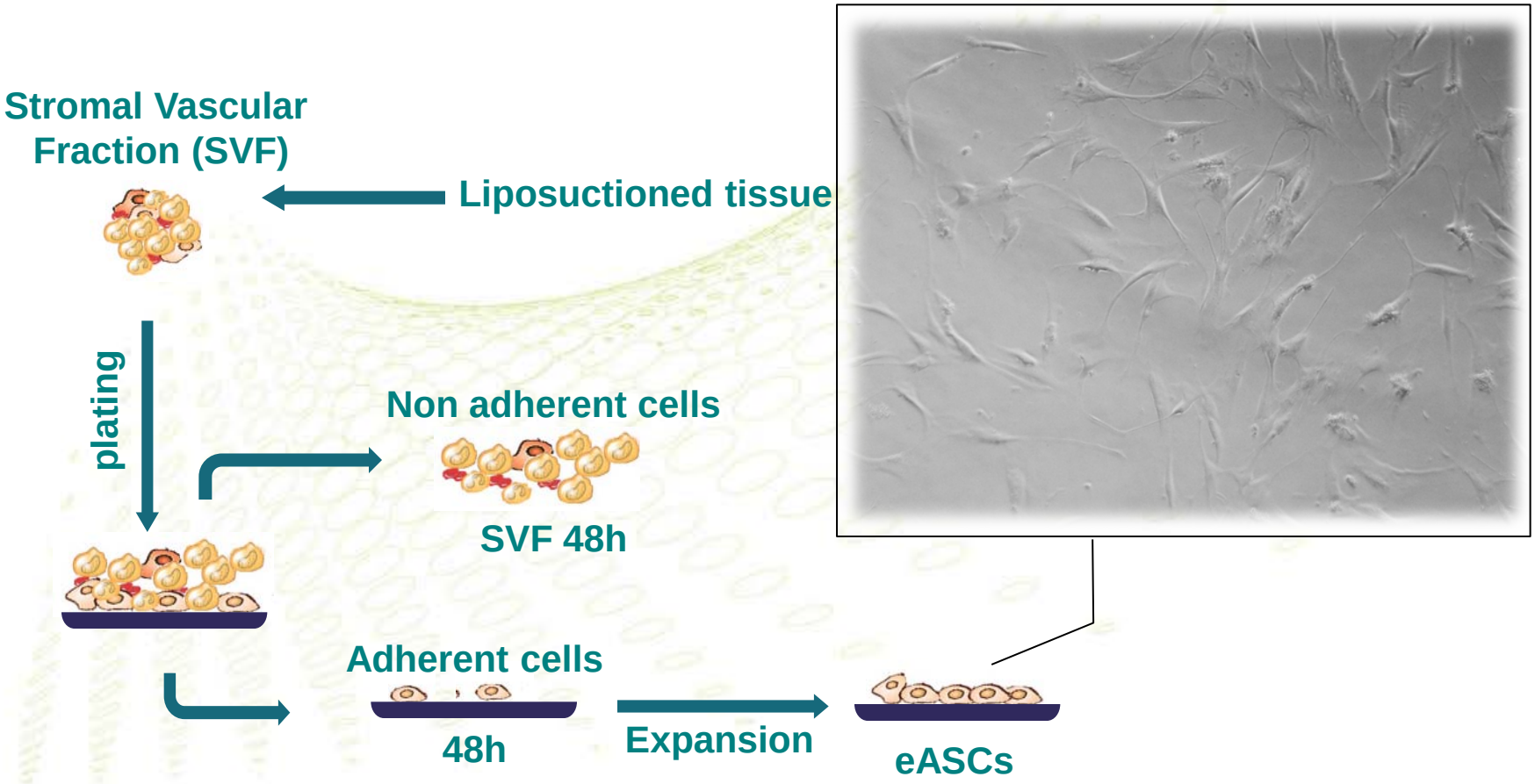
TiGenix product: expanded ASCs (eASCs)



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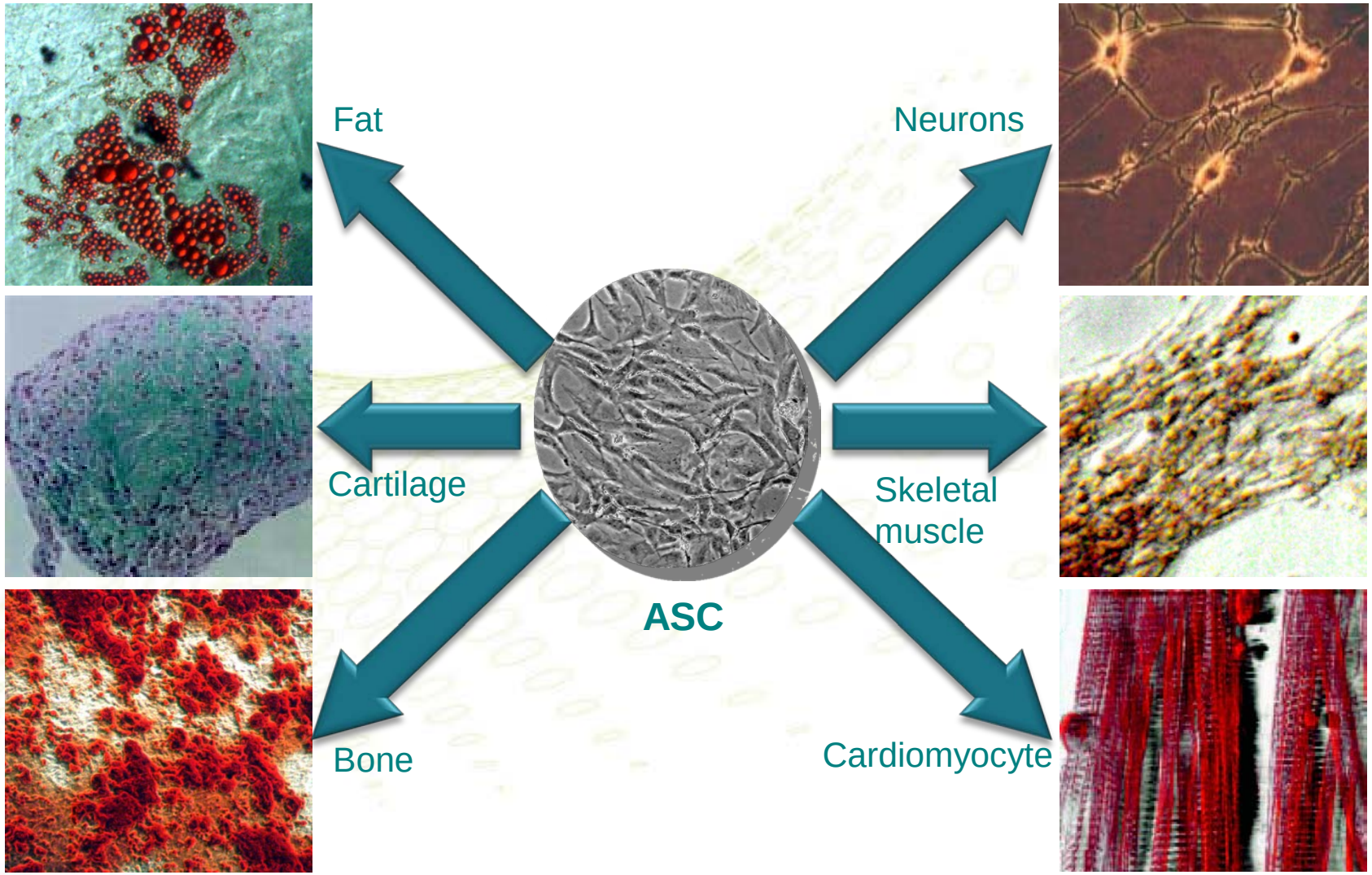
Differentiation



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Low immunogenicity: allogeneic product

Other cell types

Surface antigens

- High levels of MHC I (HLA-A, B, C)
- MHC II: depending on cell type
- Co-stimulatory molecules
  - Depending on cell type
- CD55 and CD59: depending on cell type

Other Factors

- Lack of IDO induction

MSCs

Surface antigens

- Low levels of MHC I (HLA-A, B, C)
- Lack of MHC II (HLA-DR, DQ, DP)
- Lack of co-stimulatory molecules
  - CD40 (TNFR), CD80 (B7-1), CD86 (B7-2)
- High levels of CD55 (DAF) and CD59 (Protectin) => protectors of complement associated lysis

Other Factors

- Strong IDO induction

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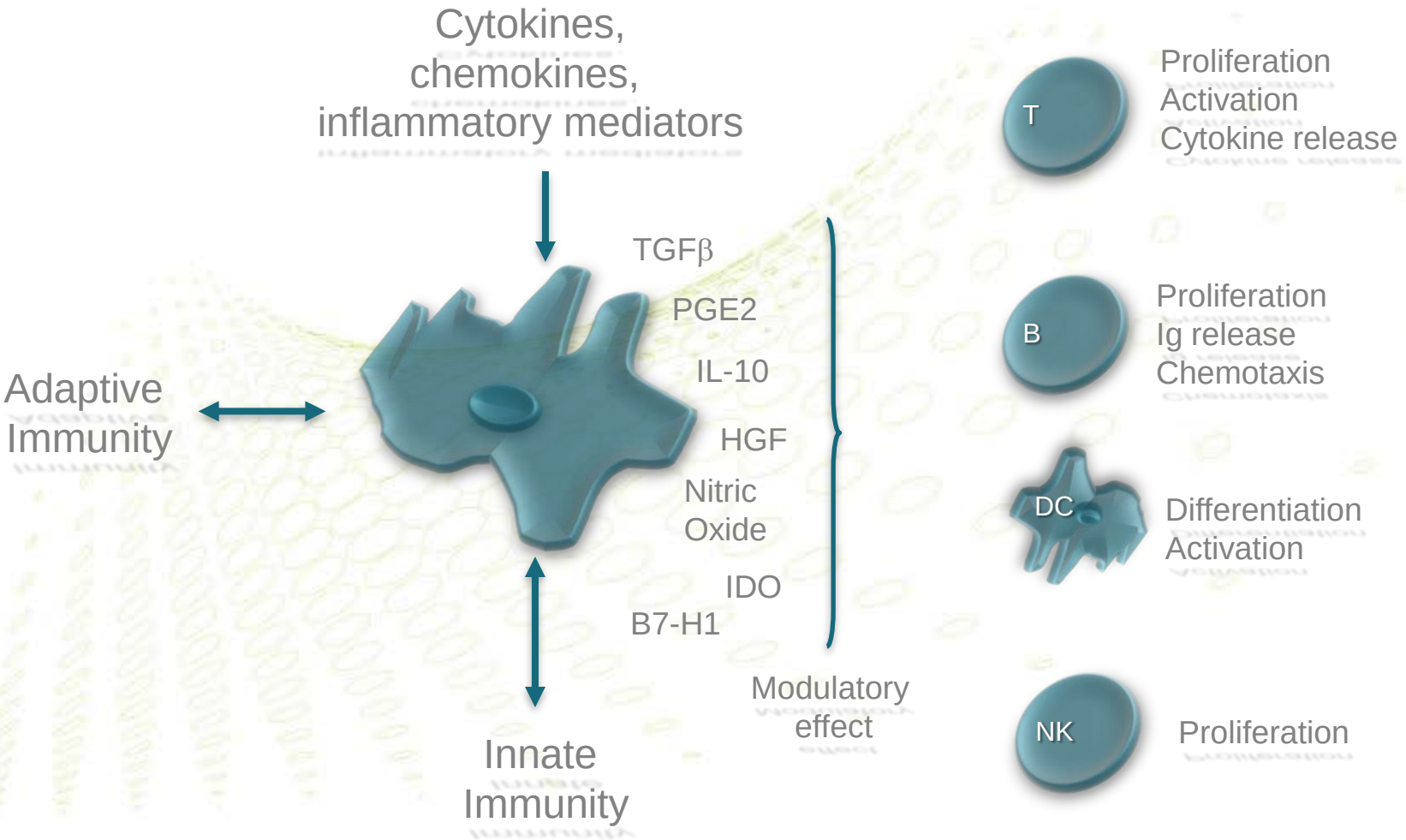
Modulation of immune responses: eASCs are primed by inflammatory environment



(Modified from Stagg, 2007)

Increasing interest on MSCs as a therapeutic tool

http://www.clinicaltrials.gov

Search term: Mesenchymal stem cells => 215 trials (Feb 2012)

- Secondary Progressive Multiple Sclerosis
- Graft Rejection and Graft Versus Host Disease
- Diabetic Foot
- Primary Sjögren's Syndrome
- Chronic Allograft Nephorpathy
- Type 1 Diabetis
- Subclinical Rejection (Organ Transplants)
- Moderate-to-Severe Crohn's Disease
- Ischemic Stroke
- Lupus Nephritis
- Sytemic Lupus Erythematosus
- Systemic Sclerosis
- Chronic Critical Limb Ischemia
- Compex Peri-anal Fistula
- Chronic obstructive Pulmonary Disease
- Inflammatory Response After Muscle and Skeleton Trauma (IRAMST)
- Osteonecrosis of the Femoral Head
- Liver Cirrhosis (injection of progenitor of hepatocyte derived from Mesenchymal stem cell)
- Treatment of Articular Cartilage Defects
- Cardiac Surgery
- Myocardial Ischemia
- MSCs in AMI (Acute Myocardial Infarction)
- Parkinson's Disease
- Osteogenisis Imperfecta
- Oestoarthritis
- Epidermolysis Bullosa
- Regeneration of Peridontal Tissue
- Intra-Articular Injection Following Meniscectomy

- ↑ **100% in 2 years!**

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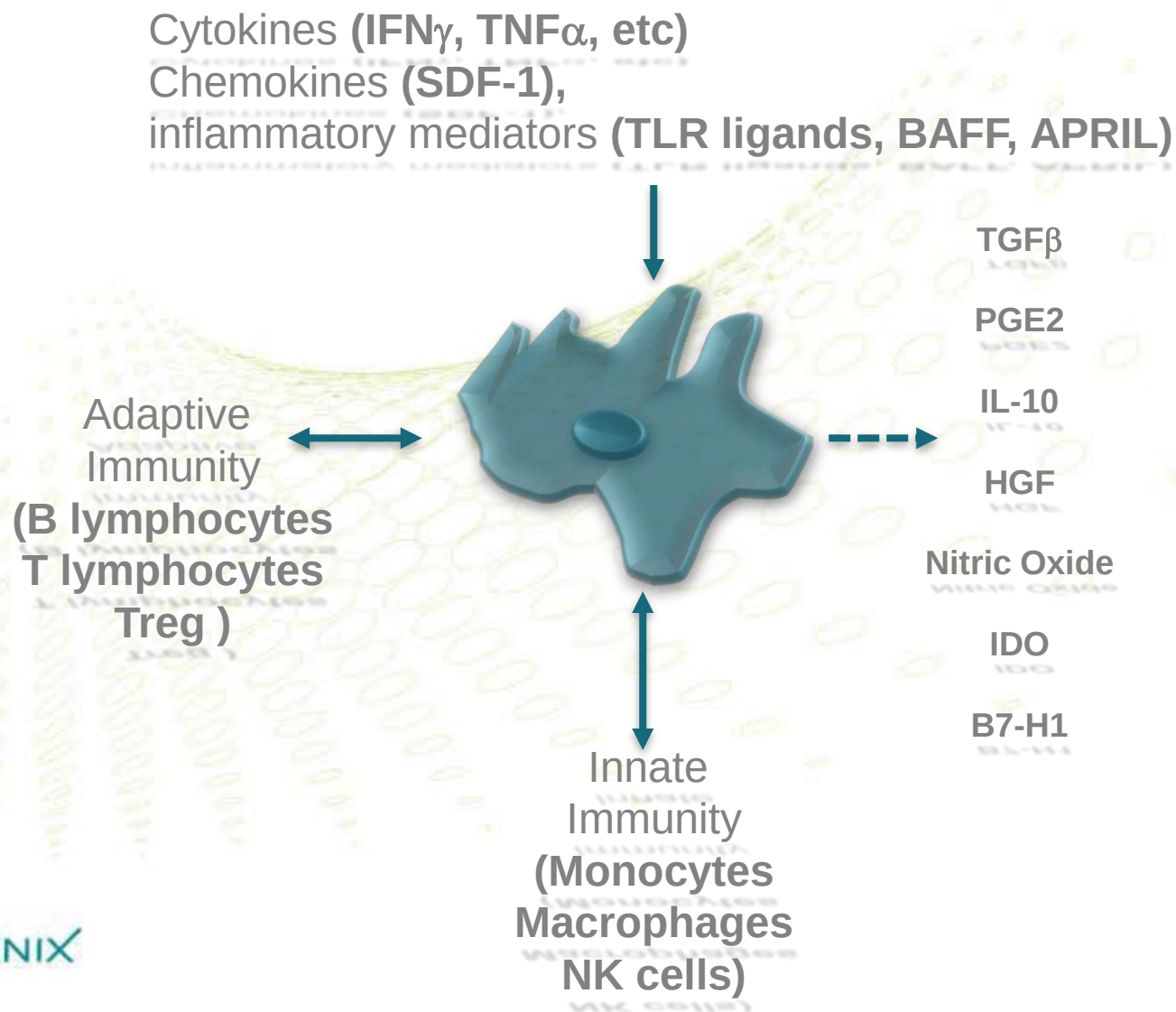
Modulation of immune responses: in vitro TiGenix research activities



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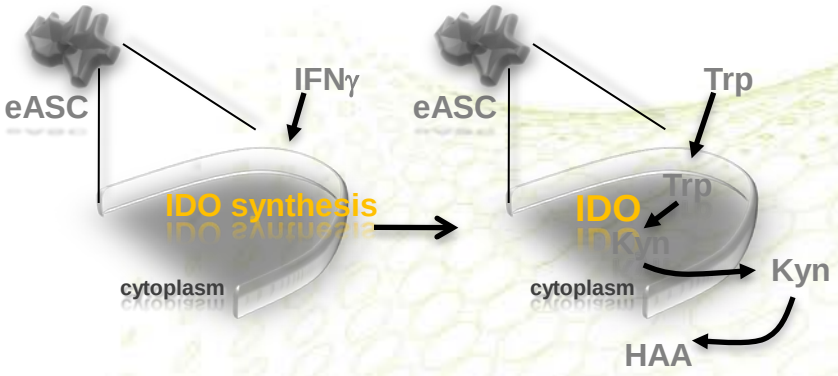
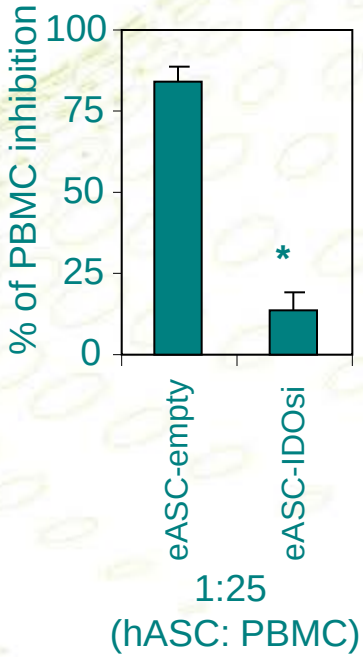
IFNγ induction of IDO enzyme is involved in the immunomodulatory property of eASCs

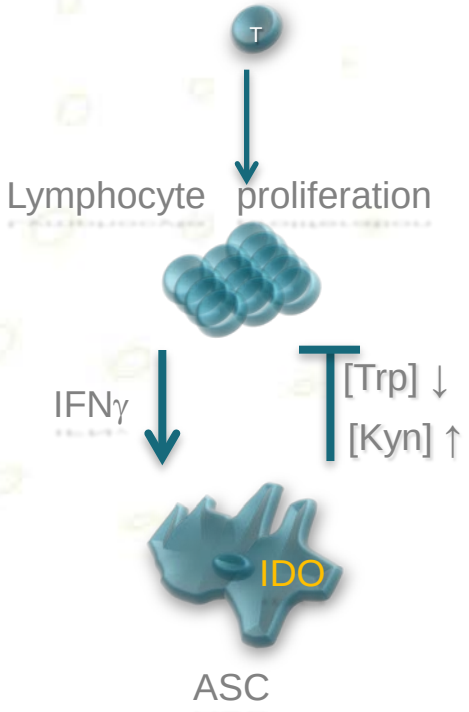
Indoleamine 2,3 dioxygenase activity: a Trp catabolizing enzyme



Prevention of T cell–driven complement activation and inflammation by tryptophan catabolism during pregnancy

Andrew L. Mellor[1], Jayabalan Sivakumar[1], Phillip Chandler[1], Kimberly Smith[1], Hector Molina[2], Dailing Mao[2] and David H. Munn[3]

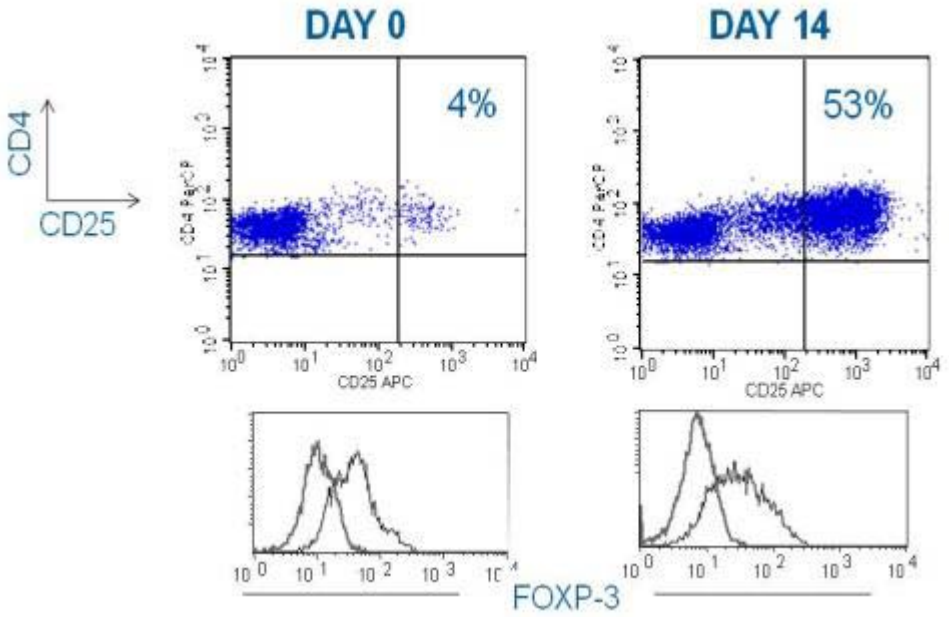




(DelaRosa et al, Tissue Engineering 2009)

eASC induce generation of Treg cells

After culture with eASCs, CD4+CD25high and FOXP3+ Treg are induced



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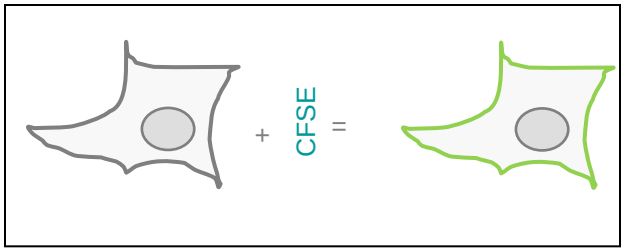
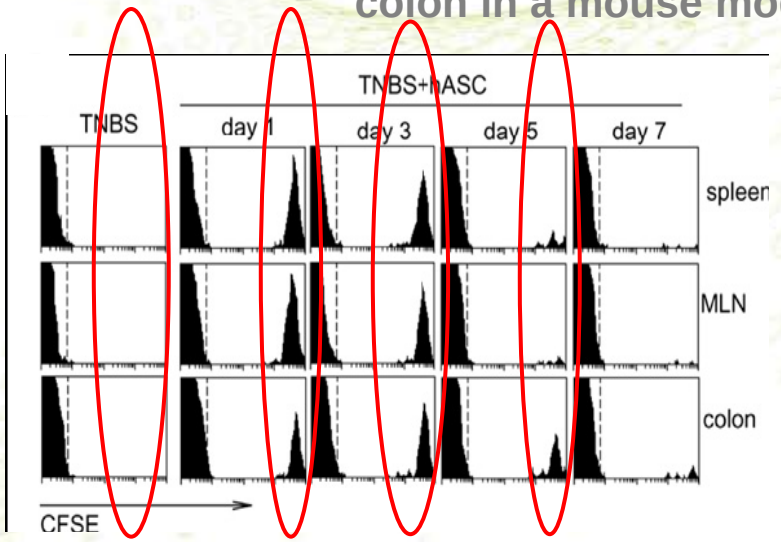
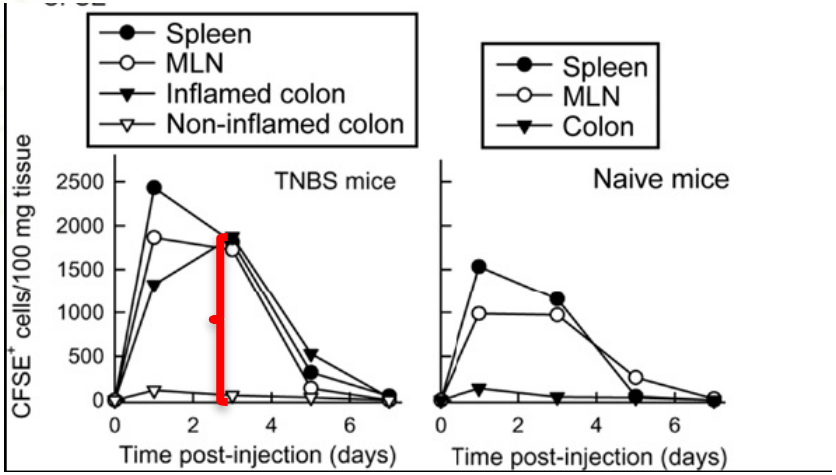
eASCs migrate to lymphoid organs and preferentially to inflamed tissue



Labeling of eASCs with CFSE allows further detection by flow cytometry

CFSE-eASCs can be detected in lymphoid organs and inflamed colon in a mouse model of colitis

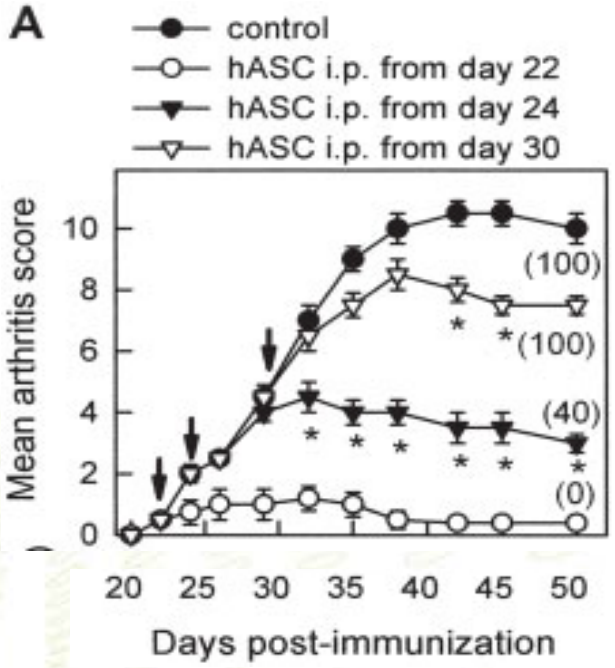




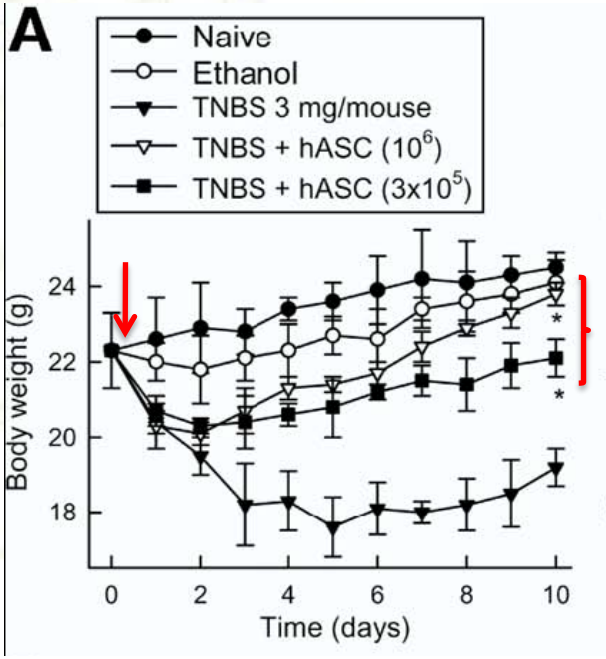
González et al. Gastroenterology 2009

Human eASCs show therapeutic effect in experimental animal models of inflammatory diseases

arthritis



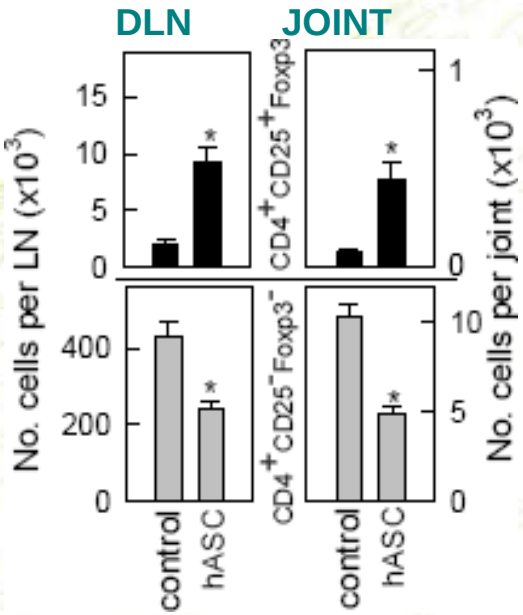
colitis



González M.A., et al 2009

Therapeutic effect of eASCs is mediated by the generation of regulatory T cells

Increased numbers of Treg in treated mice



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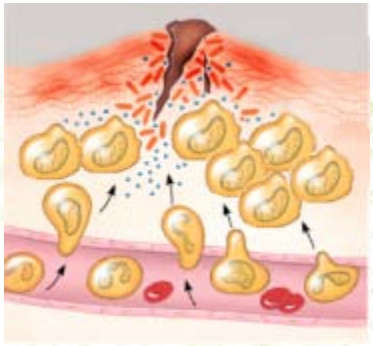
DLN: Draining Lymph Nodes

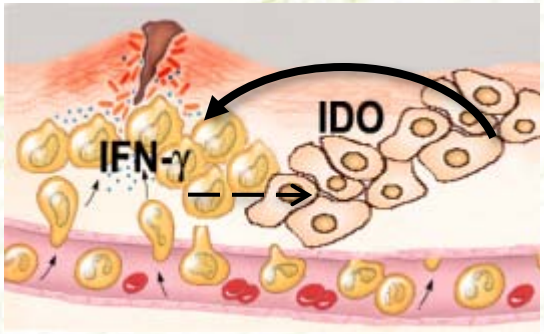
González M.A., et al 2009

Mechanism of Action: local therapeutic effect

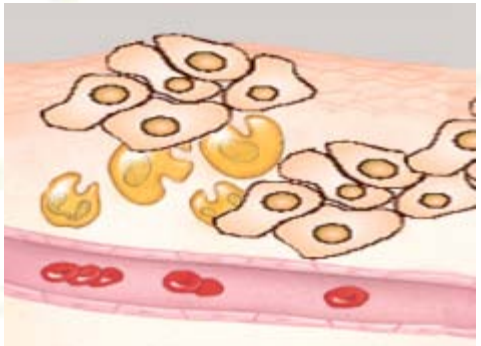
LOCAL ANTI-INFLAMMATORY EFFECT



Chronic Inflammation
Migration and proliferation of immune cells
Production of inflammatory mediators



eASC migrate to sites of inflammation
Activation by IFN-g
Induction of IDO expression
Suppression of lymphocyte proliferation
Reduction of pro-inflammatory mediators



Elimination of activated lymphocytes
Elimination of inflammatory mediators
Healing and repair

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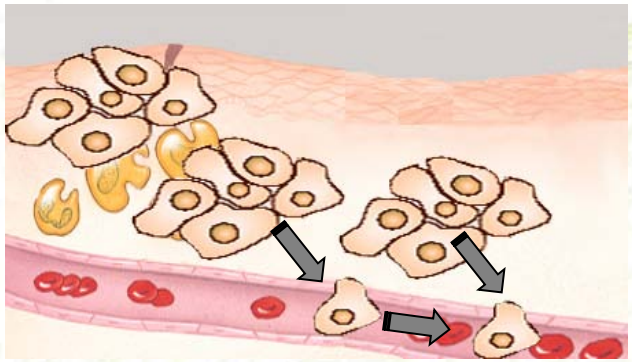
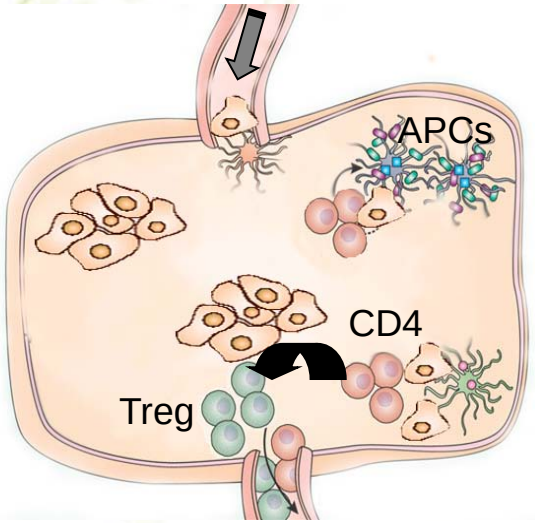
Mechanism of action: Systemic immunomodulatory effect

SYSTEMIC IMMUNOMODULATORY EFFECT





Migration

Active movement out of a local environment
eASC reach Lymph nodes through
Lymph system and/or blood stream

Immunomodulation

Migration into secondary lymph organs
Physical contact with APCs and T/B cells
Induction of new Treg cells and/or
Selective expansion of Treg cells

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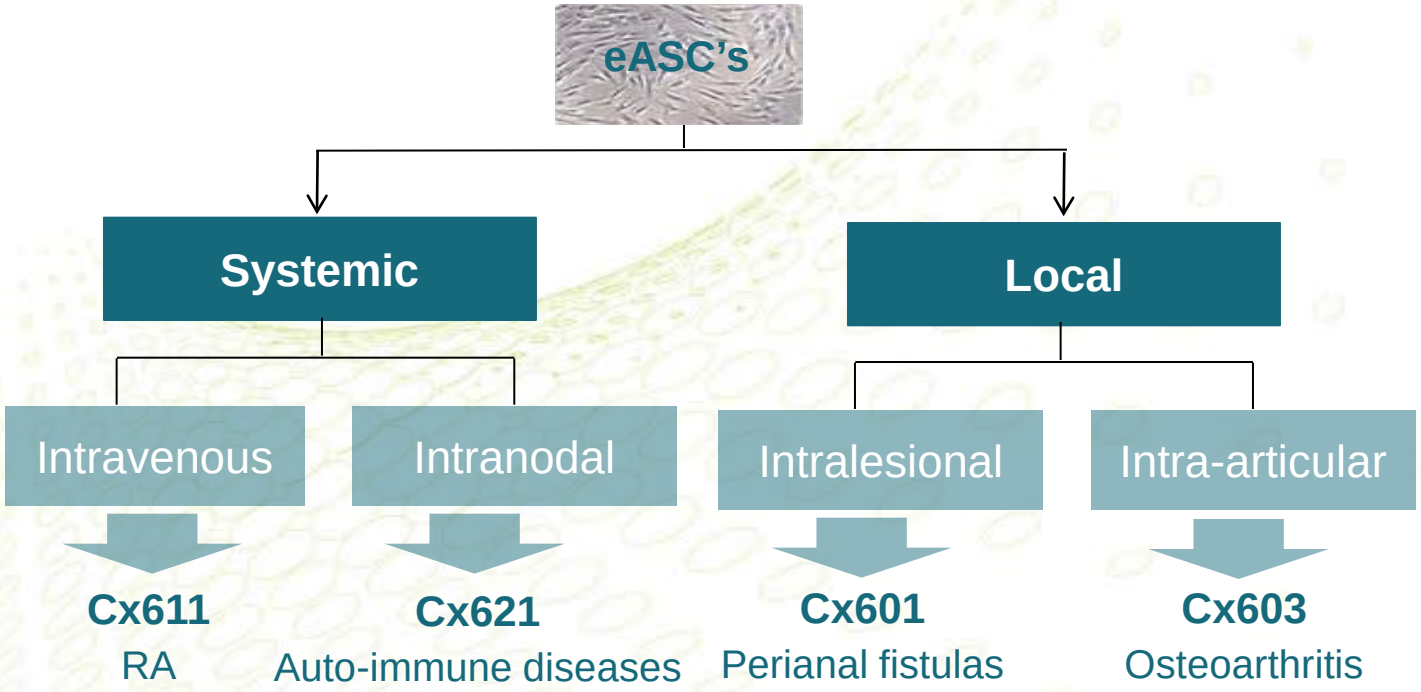
TiGenix ASC-based pipeline covers all major routes of administration



Platforms supported by solid pre-clinical and CMC packages, manufacturing experience and safety data

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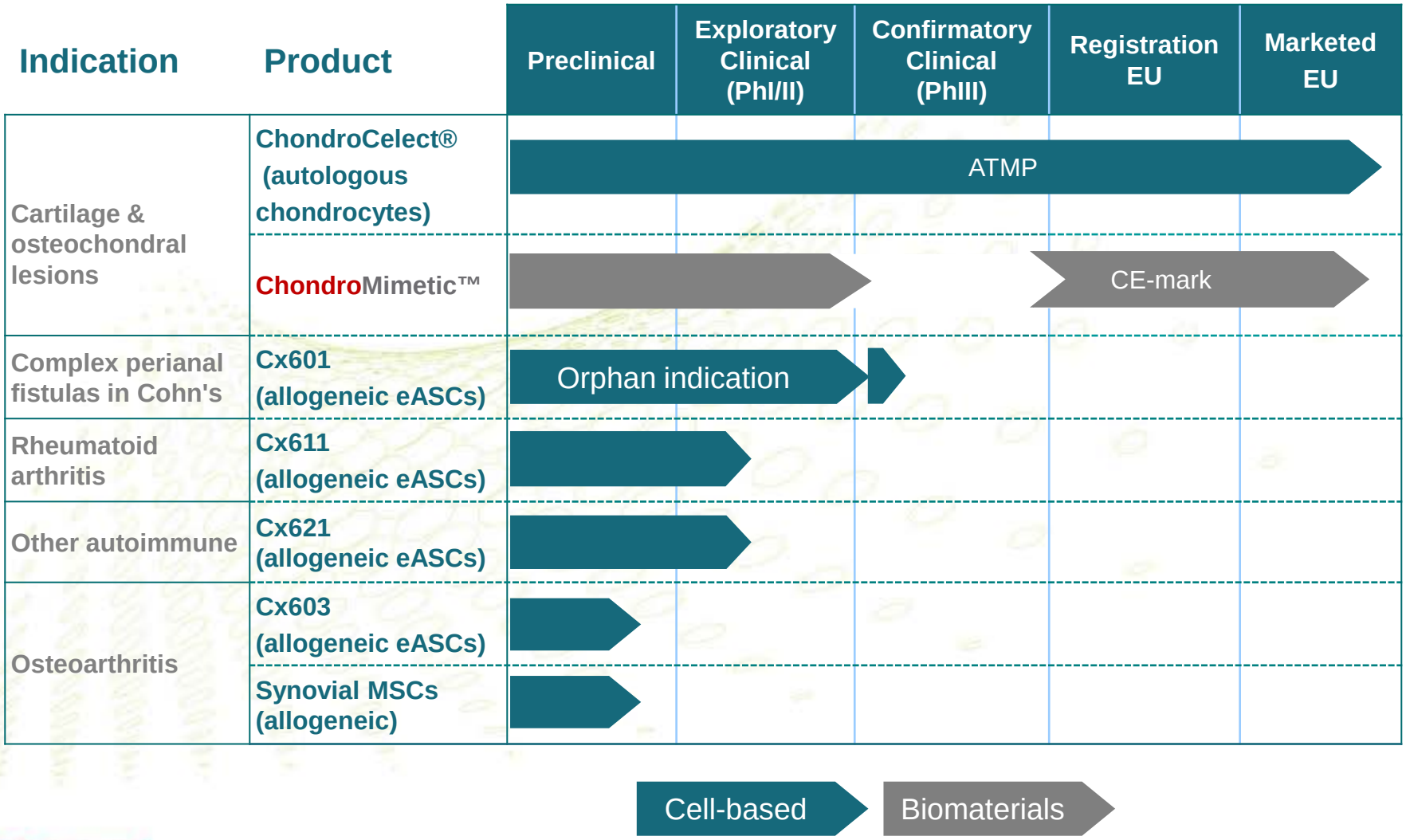
TiGenix: Current pipeline



TiGENIX * Product commercialized under CE marking

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