



INSTITUT HOSPITALO UNIVERSITAIRE

Immunothérapies innovantes appliquées aux maladies auto-immunes



Subventionné dans le cadre
du plan France 2030



UNIVERSITÉ DE
MONTPELLIER

Inserm

Avec le soutien de



Autoimmune diseases: the unmet medical need

PREVALENCE IS INCREASING

- Autoimmune diseases affect 15 million European citizens
- 4% population
- In the top ten causes of death in women under the age of 65

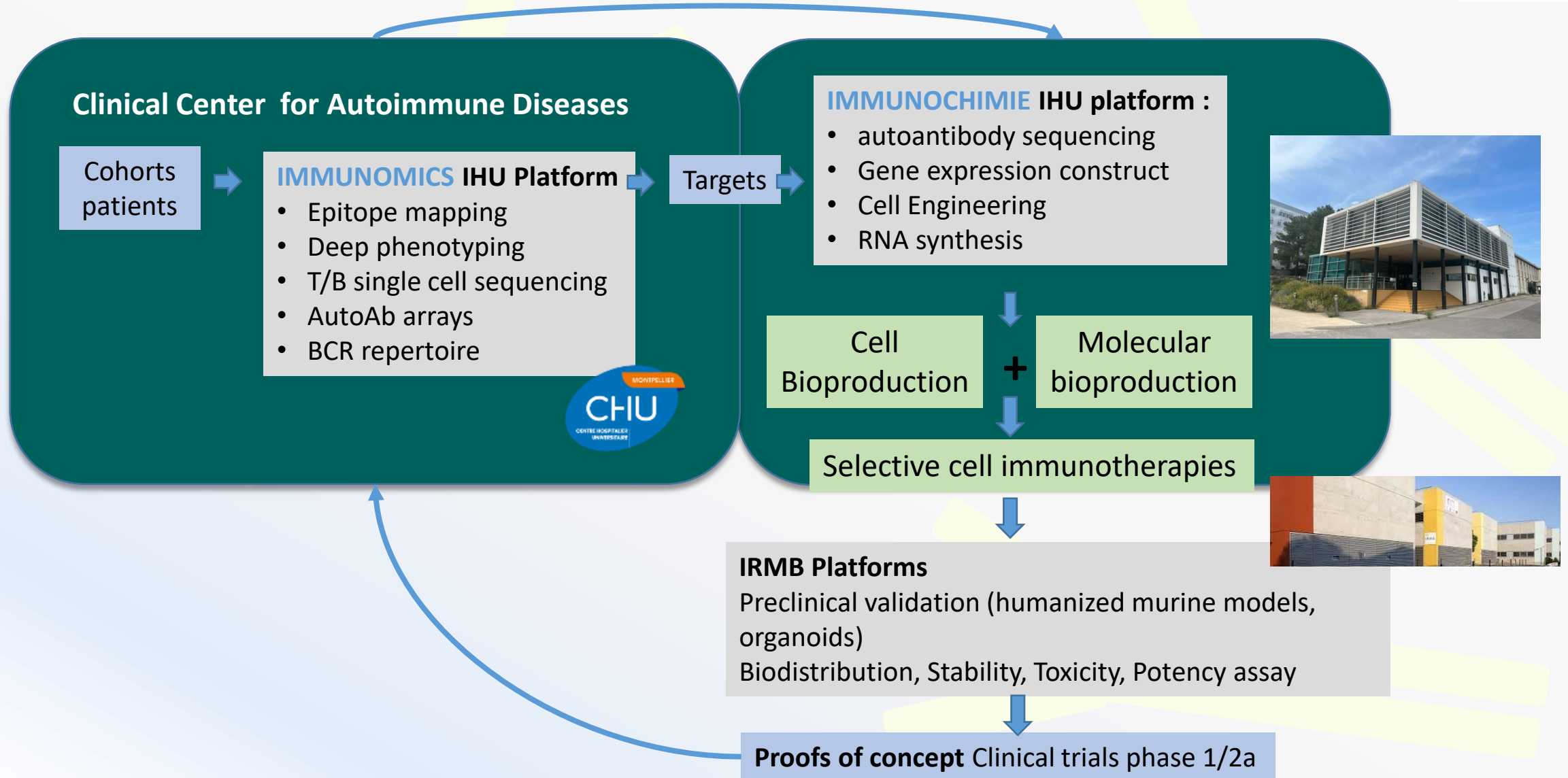


CHALLENGES

- Change the prognosis
- Integrated care path
- Identify biomarkers for patient stratification
- Propose definitive correction of immune dysfunction
- precision biomedicine
- Biodistribution, GMP bioproduction & scale up



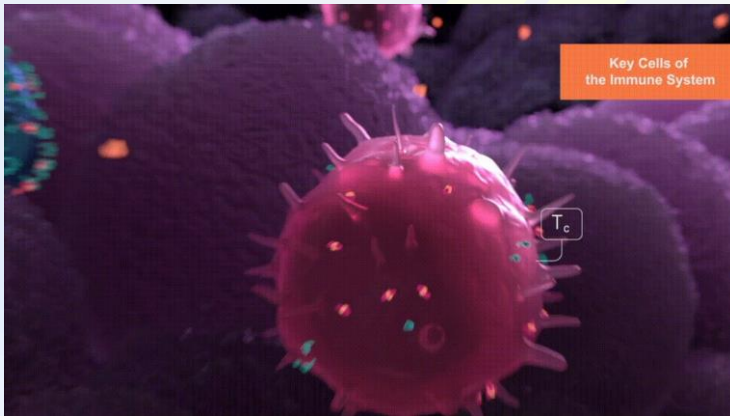
Stratégie scientifique & médicale de l'IHU



Rétablir l'homéostasie immunitaire via 3 approches sélectives

1.

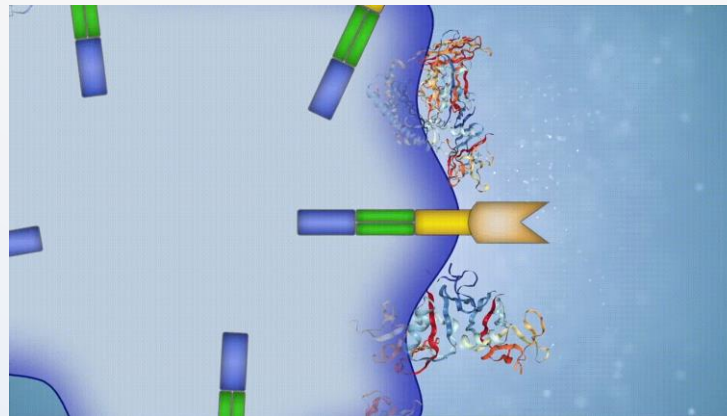
Régulation de la réponse immunitaire



Lupus, scleroderma, Sjogren

2.

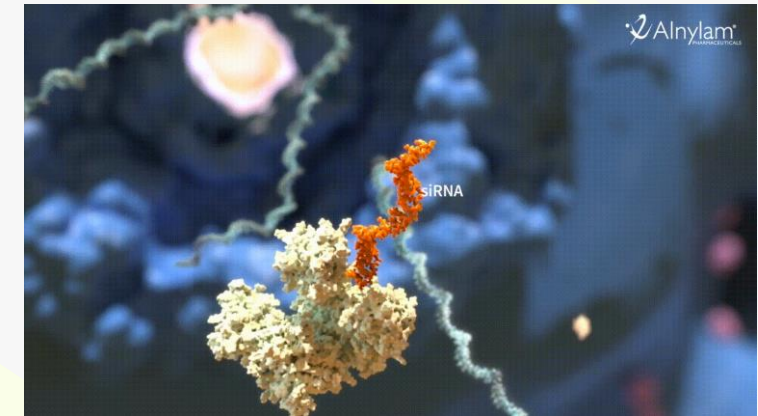
Détruction selective des lymphocytes autoréactifs



TPI, PRN, RA, Pemphigus, Wegener

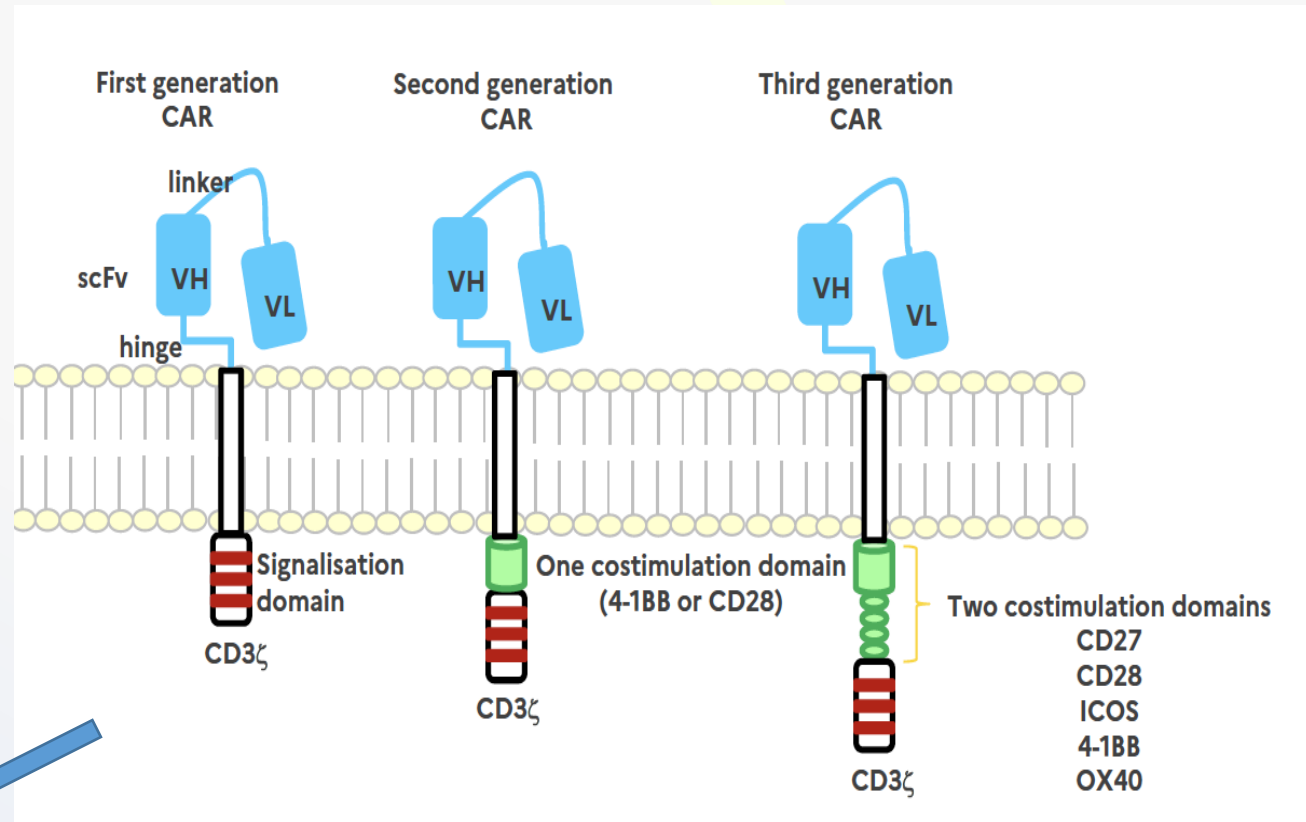
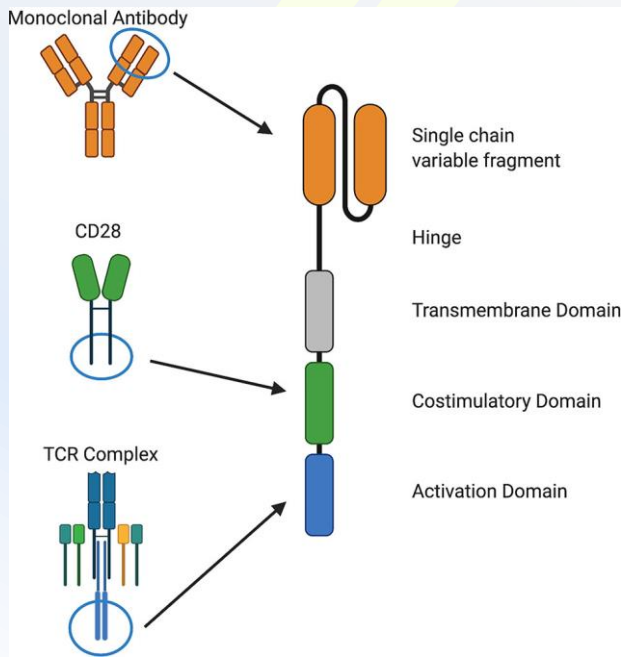
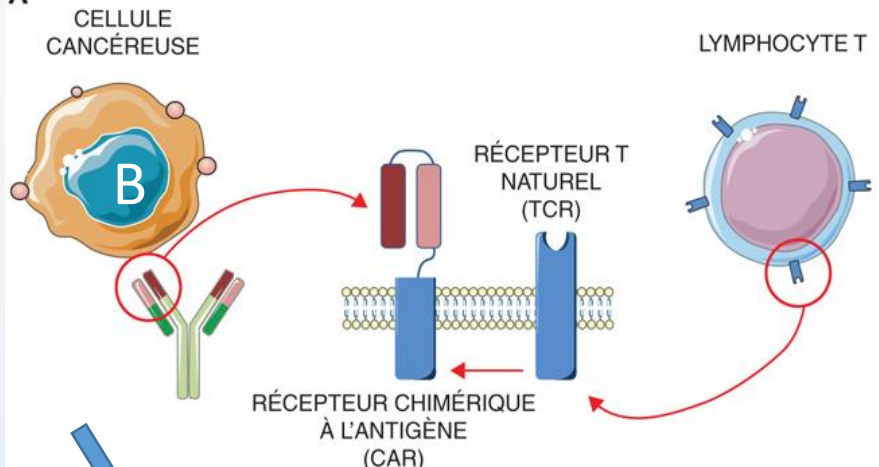
3.

Reprogrammation *in vivo* les cellules pathogènes

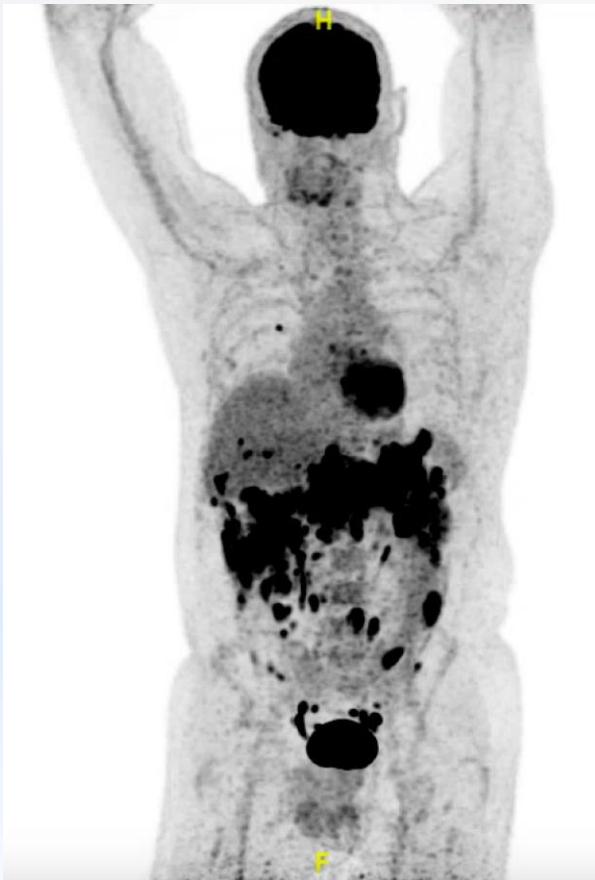


RA

CAR-T : ingénierie cellulaire pour une déplétion B



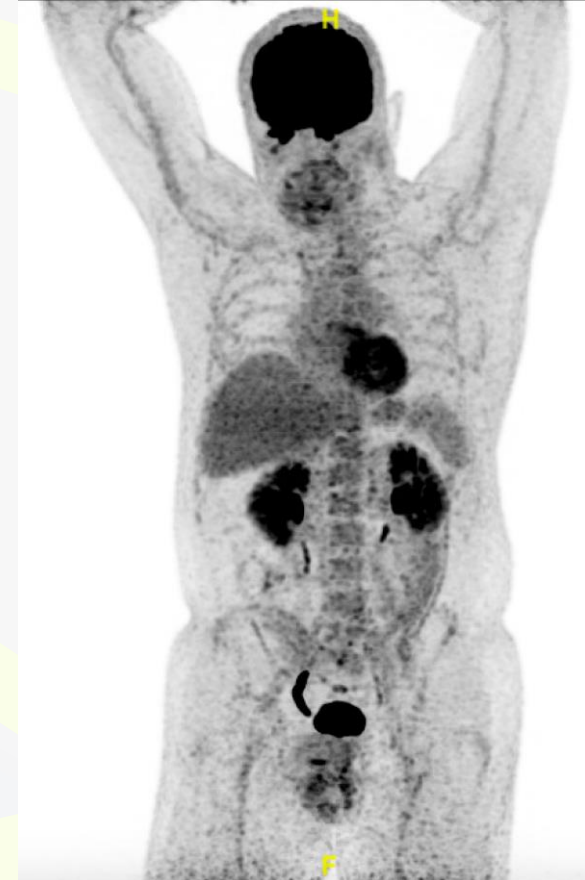
CAR-T : ingénierie cellulaire pour une déplétion B



Avant Traitement



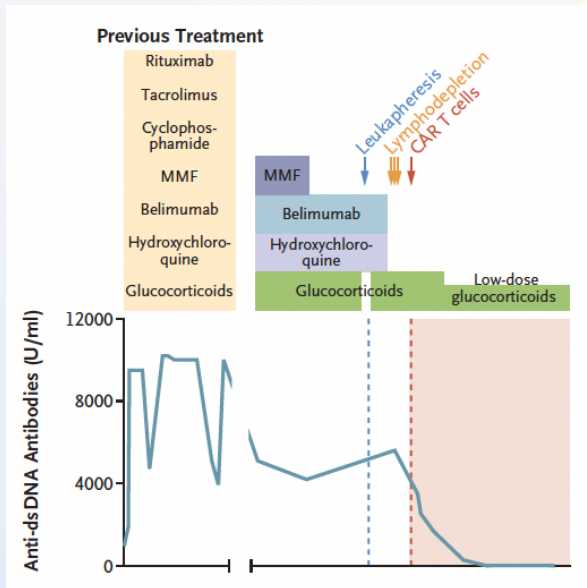
Un mois après



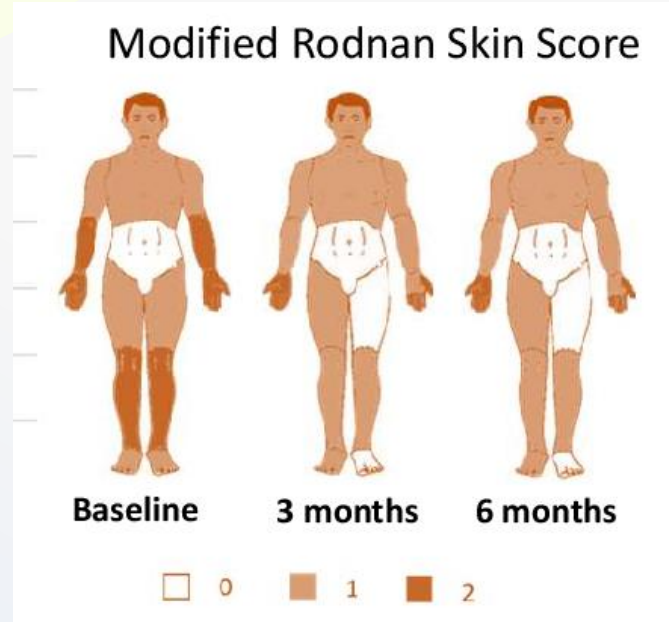
Trois mois après

Rupture technologique : CAR T cells anti-CD19 dans Lupus, sclérodermie, myosite

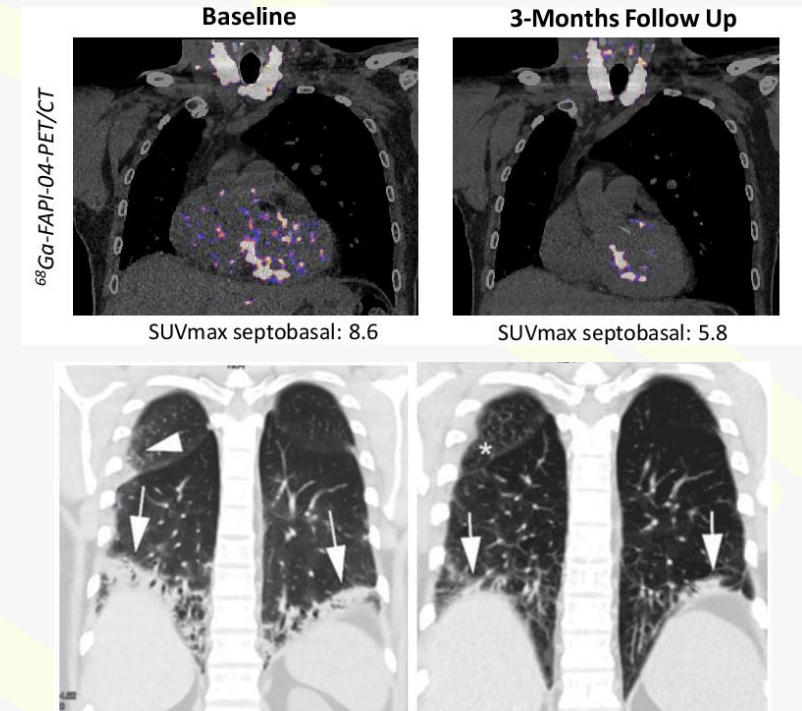
lupus



scleroderma



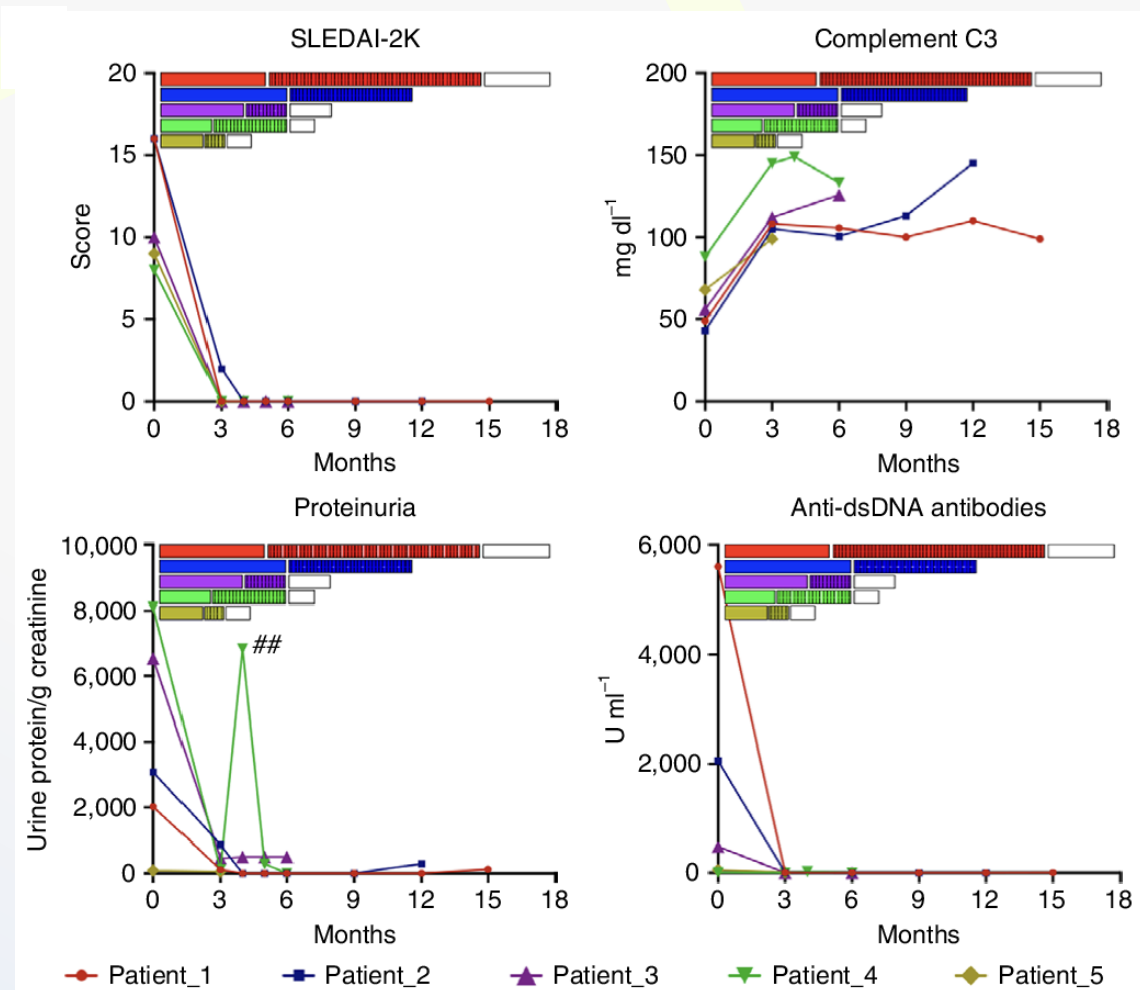
polymyositis



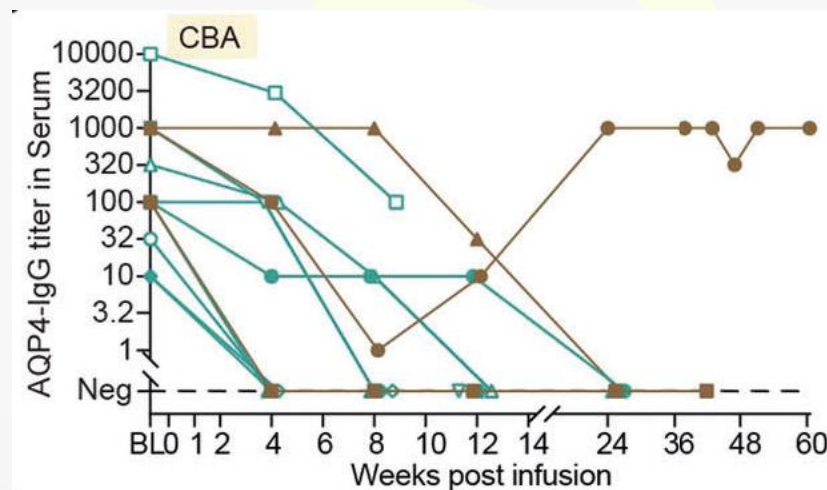
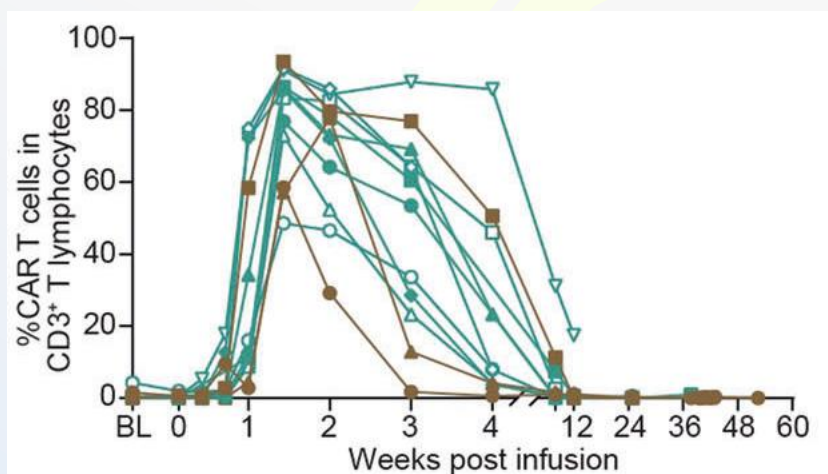
Volkl S, *New England J Med*, 2021
 Bergman C; *Ann Rheum Dis* 2023
 Muller F, *Lancet* 2023

CAR-T anti CD19 dans lupus sévère

- 5 patients
- MB-CART19.1 showed a transduction efficacy of 40% a high purity for CD4+ T cells
- Injection CART IV
- a fixed dose of 1×10^6 CAR T cells / kg
- lymphodepleting chemotherapy with fludarabine 25 mg/m²/d intravenously (i.v.) from day -5 to day -3 and cyclophosphamide 1,000 mg/m²/d i.v. on day -3 before CAR T cell infusion
- 6 months follow up



CAR-T anti BCMA dans la neuropathie autoimmune



Results : follow-up of a median 5.5 months,

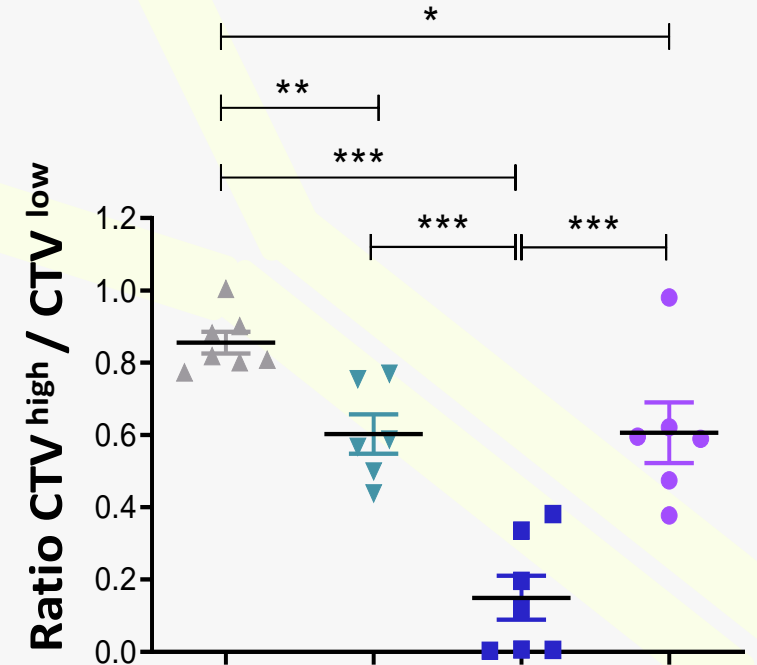
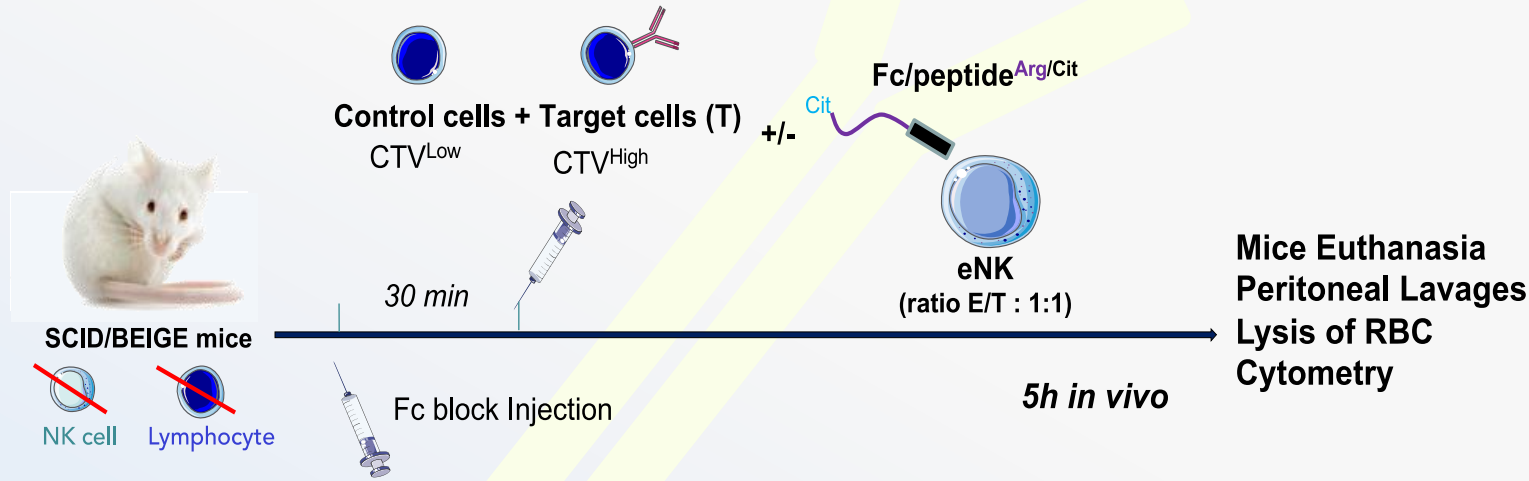
11 patients /12 had no relapse;

all reported improvement in disabilities and quality-of-life outcomes;

AQP-4 antibodies in serum decreased in 11/12.

CAR T-cell expansion was associated with responses, and persisted more than 6 months postinfusion in 17% of the patients

Armed NK-T cells : Selective B cells targeting



Target Cells	+	+	+	+
Effector Cells	-	+	+	+
Hybrids Fc/peptide	-	-	Fc/pep Cit	Fc/pep Arg

**NK cells armed with hybrid molecules
Induce ACPA⁺ B cell lysis**

- Efficient in vivo
- Specific
- Dose effect
- Reproducible

👉 **3 patents**

👉 **1 spin-off ARTHRITIS4CURE**

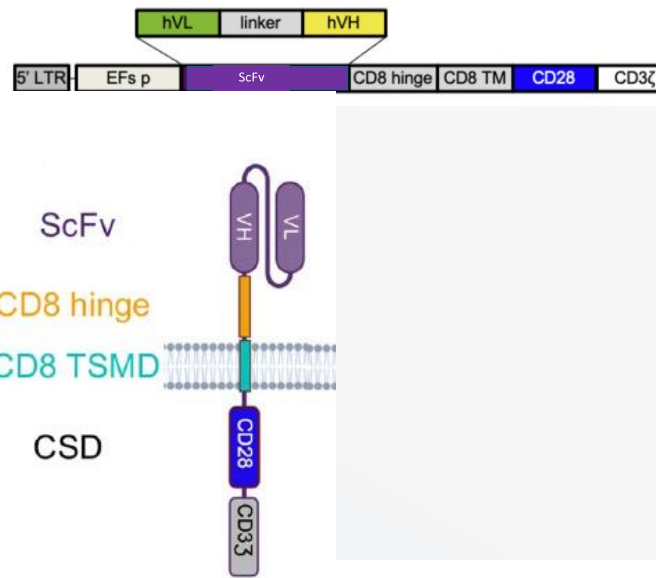
ARTHROSIS
Fondation
Recherche & Rhumatismes



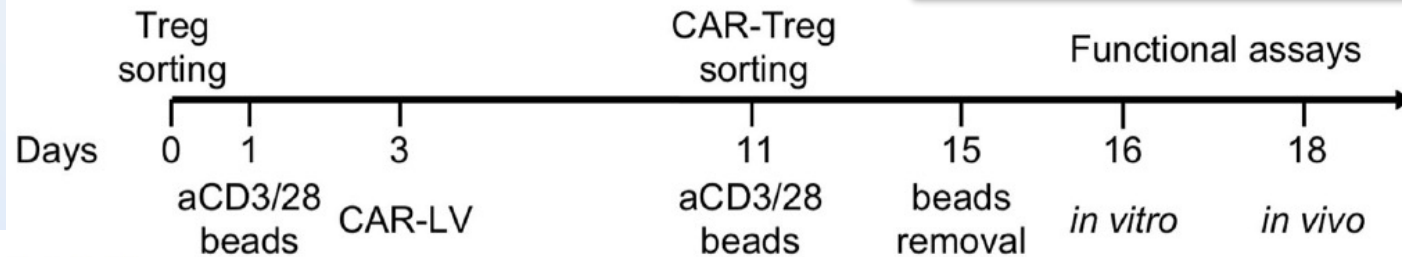
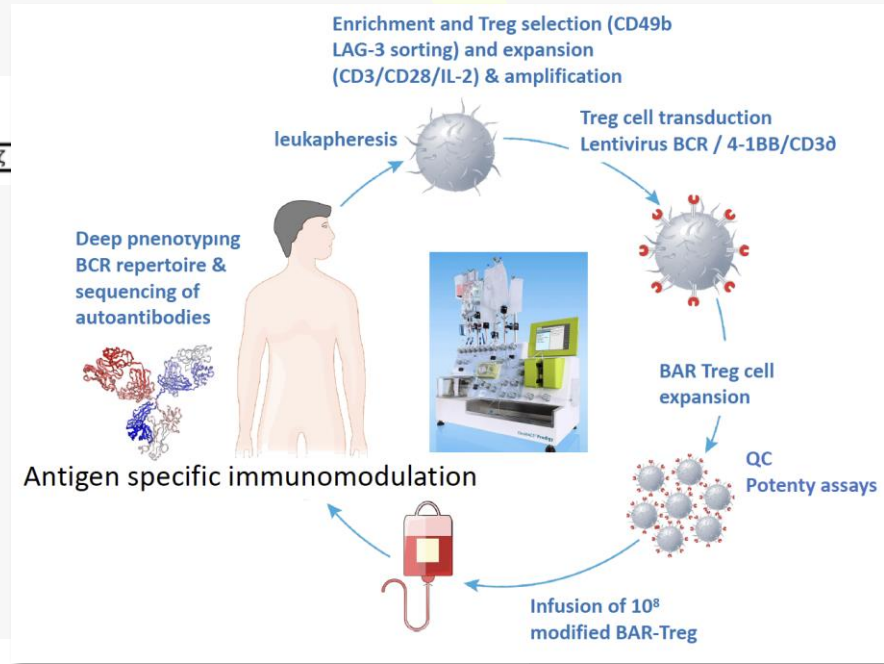
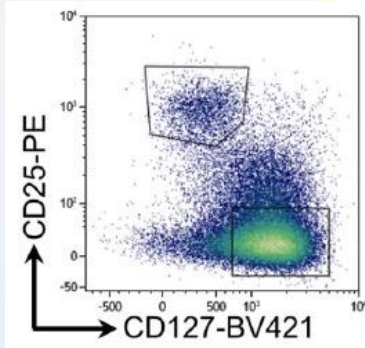
bpi**france** Inserm

Génération de CAR-Treg ciblés

Lentiviral vector manufacturing



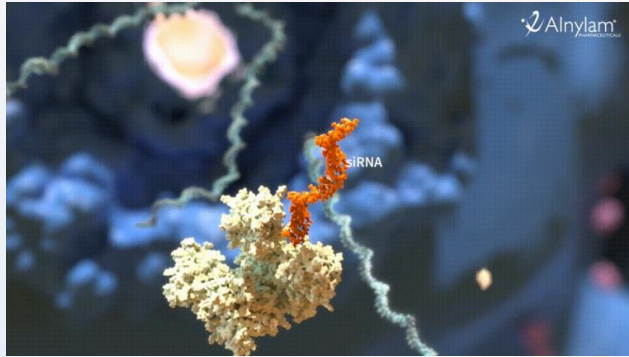
Treg cell sorting



Partners:
Inserm
IGMM
Flash Therapeutics



Nanomédecine à base d'ARN

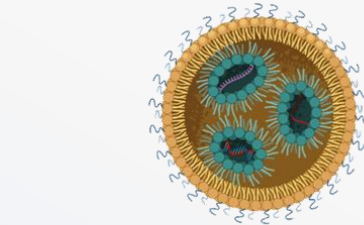
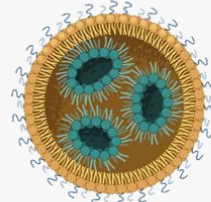


ARNs synthétiques
modifiés

Formulation lipidique
optimisée



+



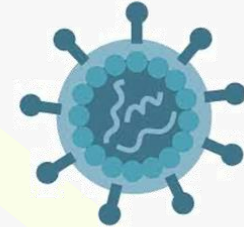
Formulation non
virale d'ARN
thérapeutiques

ARNs
biologiques

Particules lentivirales
chimériques



+



Formulation
lentivirale d'ARN
biologiques

1

2



Ciblage in vivo des macrophages

Partners:

INSERM

CHU Montpellier

Université Montpellier

Institut Charles Gerhardt Montpellier

Institut de Génomique Fonctionnelle

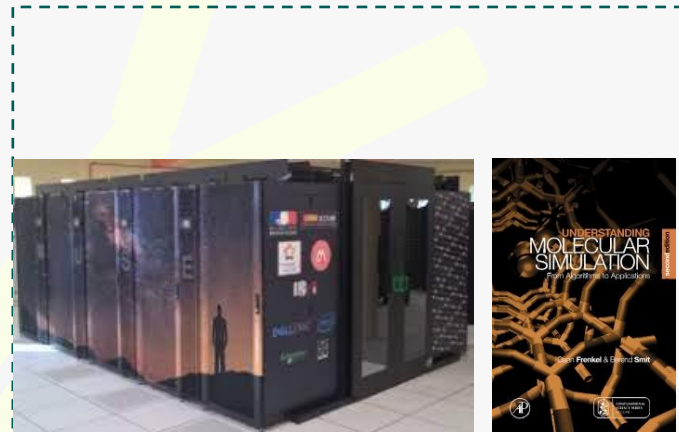
Flash Therapeutics



Modélisation de la réponse immunitaire et IA



Données biologiques (microscopie, cytométrie de flux, ...) à partir de modèles expérimentaux (in vitro, organoïdes et animaux)



Modèles physico-mathématiques pour le test et la prédiction de la dynamique des populations cellulaires (L2C-IMAG) :

- modèles à compartiments (dynamique temporelle, systèmes d'EDO sur les populations cellulaires)
- modèles spatialisés (dynamiques spatio-temporelles sur les populations cellulaires, systèmes d'EDP)
- modèles de réseaux spatio-temporels pour identifier les rôles des cellules et leurs interactions réciproques dans le développement des maladies

$$\frac{\partial u}{\partial t} = D_1 \Delta u - k_1 u(\mathbf{r}, t) + k_2 v(\mathbf{r}, t) \sum_i S(\mathbf{r} - \mathbf{r}_i(t)),$$
$$\frac{\partial v}{\partial t} = D_2 \Delta v + k_1 u(\mathbf{r}, t) - k_2 v(\mathbf{r}, t) \sum_i S(\mathbf{r} - \mathbf{r}_i(t)).$$



Données Bioinformatiques

**Modélisation physico-mathématique (approche multi-échelle)
Collaboration CINES et HDS du CHU**

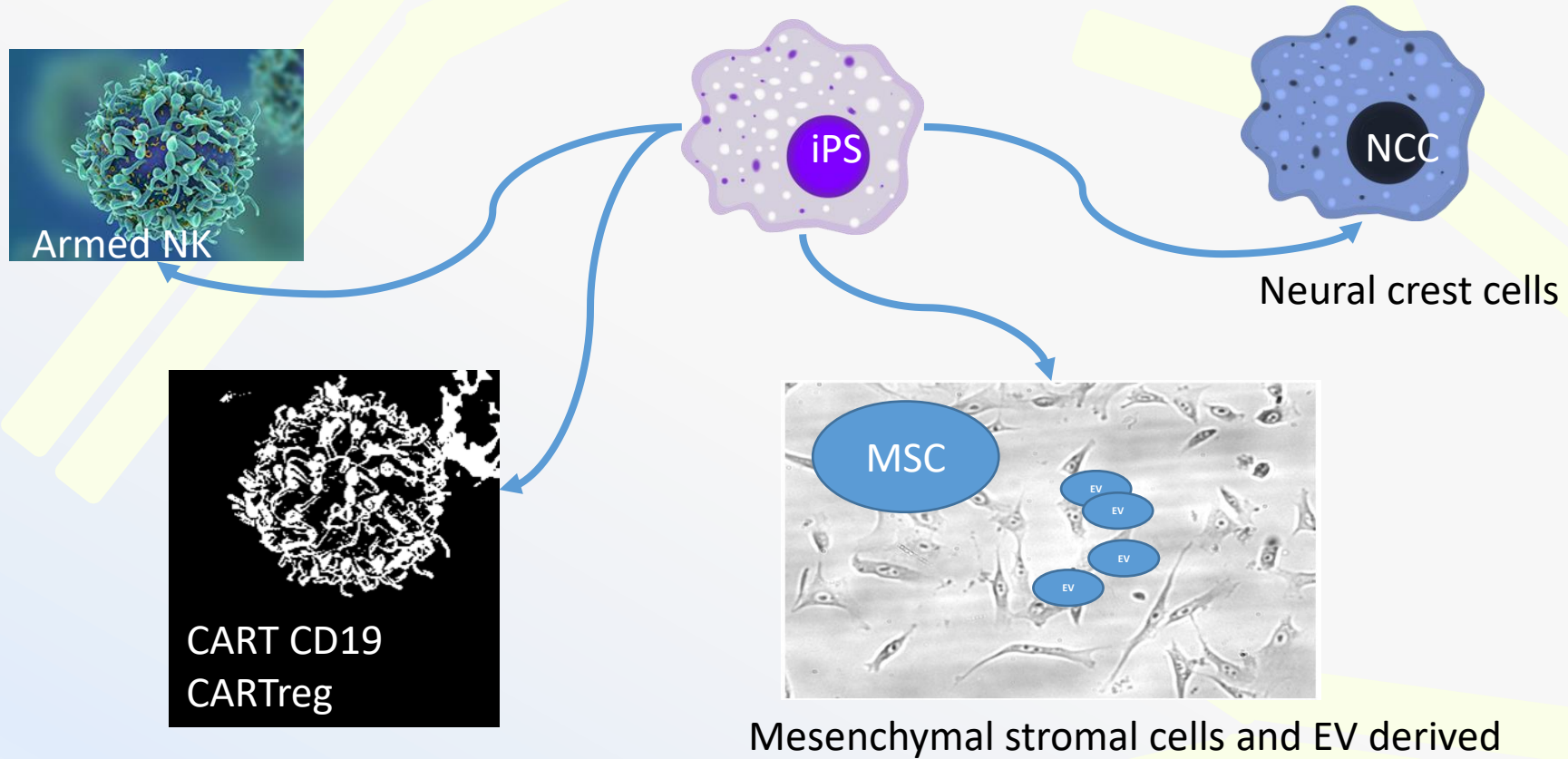
Objectif : Développer des outils numériques pour le diagnostic et la prédiction des maladies auto-immunes

Partners:

Parmeggiani A.

IMAG-L2C

Therapeutic cell types available at IHU

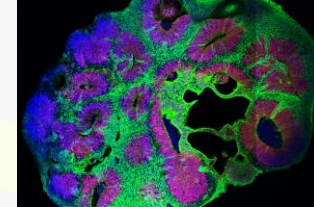


Preclinical models available at IHU

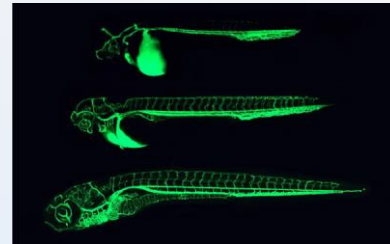
Murine models :
CIA, CIOA, scleroderma



organoids:
Joint on a chip
Pulmonary
Epidermal
brain



zebra models :
Regeneration, vascular, interactions

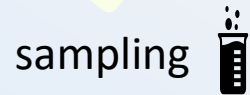
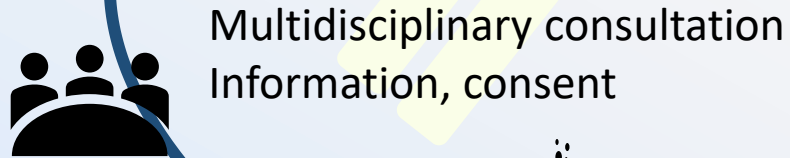
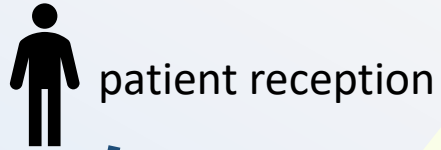
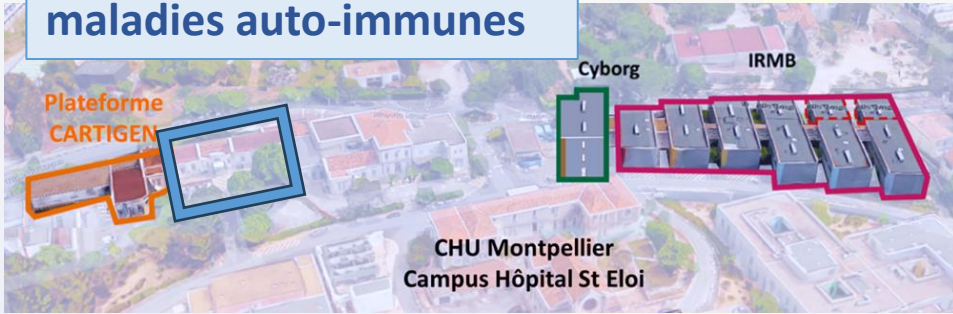


humanized models :
NGS
SCID/hu

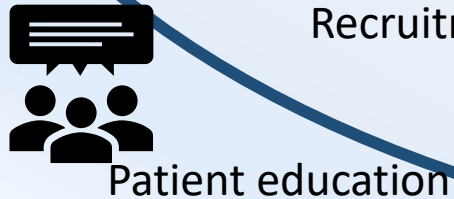


Centre Interdisciplinaire des maladies auto-immunes

Centre Interdisciplinaire maladies auto-immunes



Recruitment into a cohort



Personalized therapy



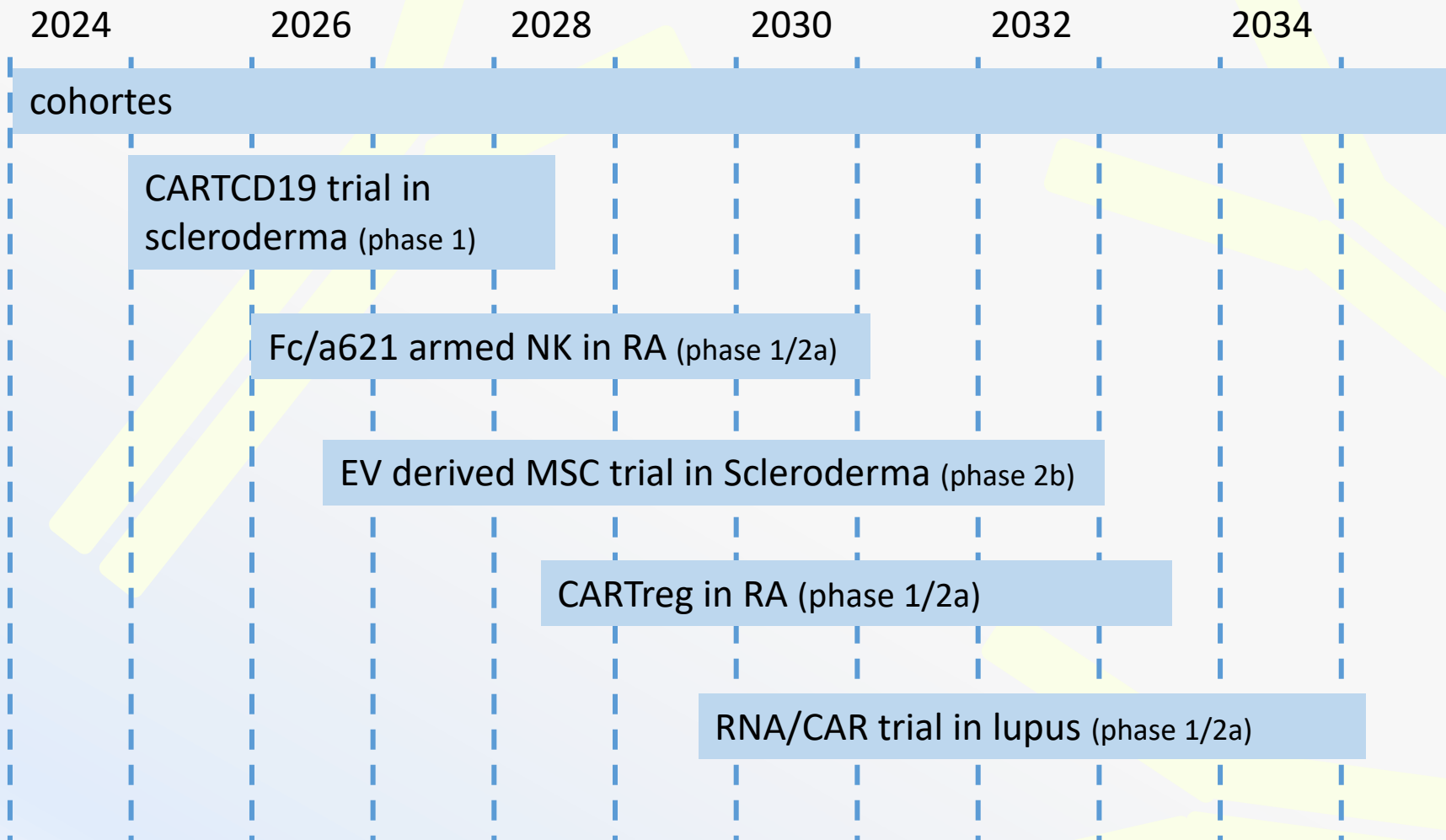
- ✓ Centre de soins : prise en charge multidisciplinaire
- ✓ accès biothérapies
- ✓ Accès au « **Deep phenotyping platform** » : BCR, NGS, VDJ, immunophenotype, epitope mapping
- ✓ Mise en place des **cohortes**
- ✓ Education thérapeutique

Deep phenotyping

- including BCR,
- NGS,
- VDJ,
- immunophenotype,
- epitope mapping



Clinical development



IHU IMMUN4CURE Montpellier



Institute for regenerative medicine & biotherapies
200 scientists, engineers and physicians

The campus

CYBORG Incubator for biotech



Centre Interdisciplinaire
maladies auto-immunes

CHU : Internal medicine, Hematology,
Rheumatology, Dermatology, laboratory, CRB



UTC : cell therapy unit, 3000 m2 clean rooms

Governance

INSERM FOUNDATION

ADMINISTRATIVE COUNCIL of the IMMUN4CURE FOUNDATION

Chaired by Pr A FISCHER



COMEX



C. JORGENSEN

DIRECTOR

Scientific coord.
S Kremmer



Administrative
Division

C. LACOMBE

- Finances
- Human Ressources
- IHU Manager
- Support services
- Technical service
- Infrastructure



Scientific
Division

F. DJOUAD

- Cellular Immunotherapy
- Molecular Medicine
- Regenerative Medicine
- Immunology & Immunotherapy
- Bioinformatics & Molecular Modelling



Medical
Division

G. CARTRON

- Clinical trials
- Regulatory issues
- Ethical issues
- Cohorts
- Coord. CRB & data
- CIMA clinical centre



Training
Division

J. DE VOS

- Call for PhD
- European Master
- Integration of teaching Unit in medical & pharmaceutical curriculum
- Traineeship coordination
- Organisation of technicians training



Valorisation
Division

TO BE RECRUITED

- Business Developer
- Interaction with SATT
- Legal issues
- Sourcing
- Valorisation and patents
- Contracts

IMMUN4CURE is the first Institute dedicated to autoimmune diseases



Clinical departments

Nephrology
Haematology
Rheumatology
Clinical immunology
Genetics
Dermatology
Internal medicine
Neurology

Interdisciplinary Center (CIMA)

- Cohorts
- Clinical trials
- Patient care
- Education

Platforms

- System Immunomics
- Biomolecule design
- RNA reprogramming

Research infrastructures

- ECELLFrance
- SAFE-IPS

Platforms

- Transcriptomics
- Proteomics
- Bioinformatics
- Organoids
- Animal facilities

Incubator hosted spin-offs
+ Industrial partners

Research teams

Industries , Biotechs & bioproduction

Filière Biothérapies Innovation Occitanie

MedVallée

National infrastructures ECELL France , INGESTEM, IFB

Sanofi, Servier, Celleasy, Flash, Sangamo, EVOTEC, medxcell



Research Teams

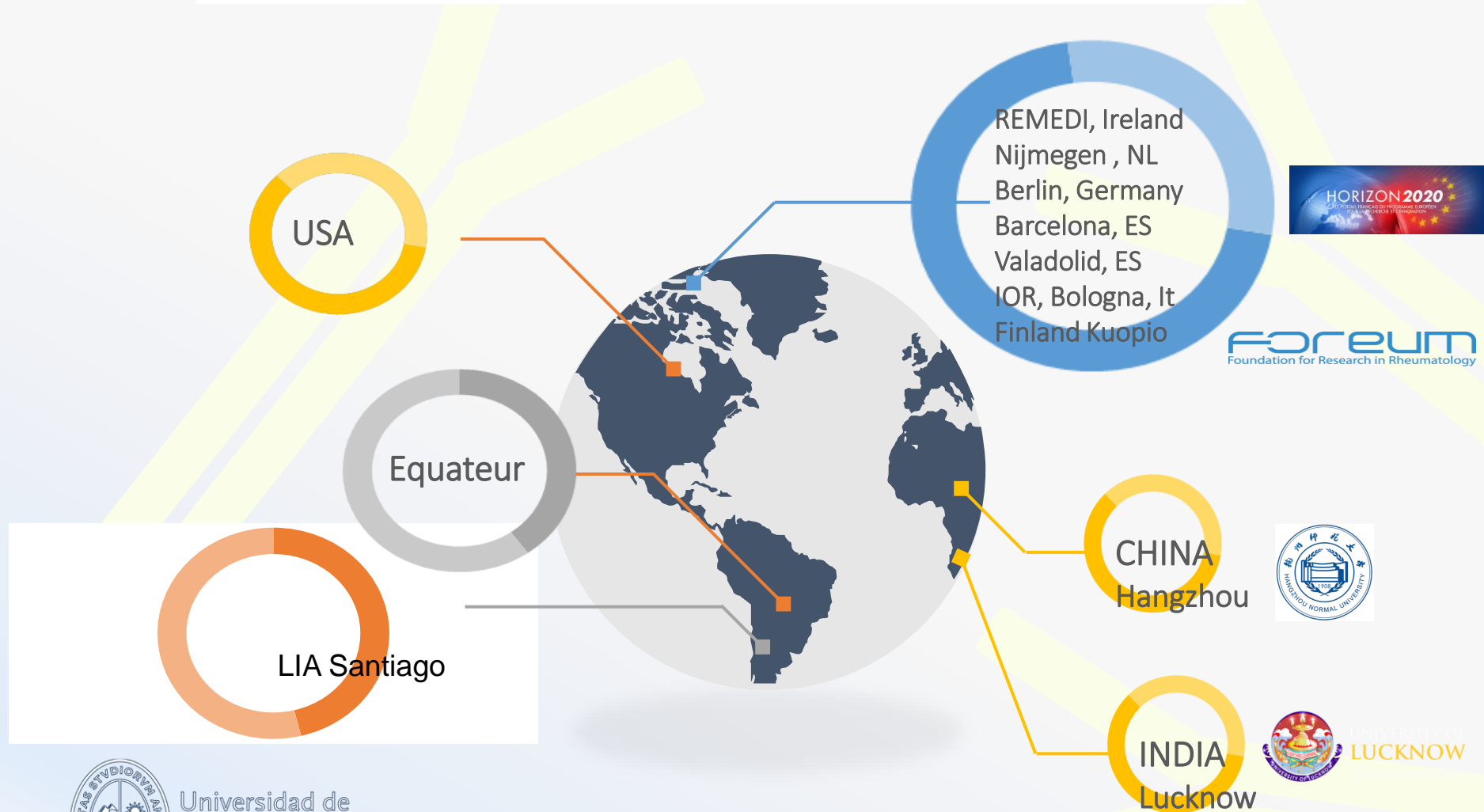
IGH Pasero, Benkirane (genomics)
IGF David, Rondard (RNA, Nanobodies)
IRMB Apparailly, Lemaitre, Villaba, Jorgensen (Immunology, NK, iPS, MSC, EV)
IRCM Bonnefoy, Martinau (Ab, molecular bio)
PHYMEDEX Lacampagne (models)
ICGM Morille (RNA encapsulation)
IGMM Zimmerman, Taylor (CART)
IBMM Subra, Vasseur (mRNA)
LIRM, IDESP, IMAG, L2C (modelling, data management)

Ambition to accelerate the French biotherapy strategy

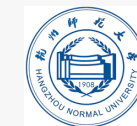
The Partners



International Partnerships and Academic interactions



Universidad de
los Andes



LUCKNOW