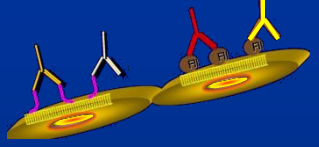
Université de Tlemcen Faculté de médecine

Syndrome des antiphospholipides « Quoi de neuf »

Professeur K ALLAL TAOULI
Hémobiologie et transfusion sanguine

5 th séminary of « LAREDIAB »
11 th CONGRESS OFAMIWIT Friday 9& Saturday 10 December 2022



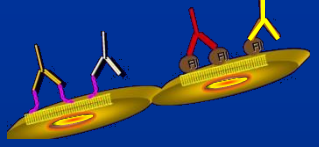
INTRODUCTION

SAPL (syndrome de Hughes) Pathologie auto-immune systémique./clinique et épidémiologie mieux connues:

événements thromboemboliques et/ou de complications obstétricales récurrentes et

présence persistante d'anticorps antiphospholipides (APL) (ACC LA), Anticorps anticardiolipine (aCL), et Ac anti-β2 Glycoprotéine 1 (aβ2Gp1).

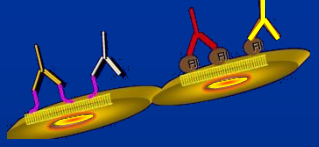
principes du diagnostic biologique et aborde la relation entre risque de manifestations cliniques et tests biologiques



SAPL/Introduction

Englobe toutes les disciplines .

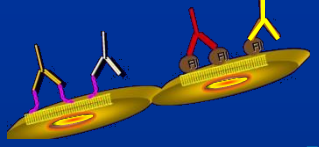
Cause traitable de perte de grossesse, et a changé la face de ***l'obstétrique.***
En neurologie *cause importante d'AVC, migraine, convulsions, perte de mémoire…*
En cardiologie *, cause fréquente de crises cardiaques chez le sujet jeune , c'est aussi une piste dans l'étude de* ***l'athérome accéléré…..***
– fracture osseuse idiopathique, angine abdominale, hypertension vasculaire rénale, ulcères de jambe……



SAPL

HISTORIQUE

- **1906: Wasserman/ diagnostic syphilis**
- **1952: Conley/ LED et ↗ TCA**
- **1963: Bowie /thrombose et LED et LA**
- **1972: Feinstein et Rapaport / LA .**
- **1980: Soulier et Boffa/(pertes fœtales et LA)**
- **1983: Harris / aCL (RIA ELISA)**
- **1983: Hughes/ Syndrome des anticardiolipines,SAPL**
- **1994: Asherson : SAPL primaire et secondaire.**
- **1996: Alarcon Segovia, Cabral : SAPL/cofacteurs**
- 1980s Detailed description of anti phospholipid syndrome (APS)
- 1990 Phospholipid binding proteins (b2GPI)
- 1990s Animal models for APS
- 1999 Classification criteria for definite APS
- 2006 Classification criteria updated



Critères de Sapporo révisés (S. Miyakis)

Classification criteria for APS

Clinical criteria:

- Vascular thrombosis
  - Arterial, venous or small vessel thrombosis in any tissue or organ (excluding superficial thrombosis), confirmed by appropriate imaging or histopathology
- Pregnancy morbidity – at least one of the following:
  - ≥1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
  - ≥1 premature births or a morphologically normal neonate before the 34th week of gestation owing to eclampsia or severe pre-eclampsia or placental insufficiency
  - ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with hormonal, chromosomal or maternal anatomic causes excluded

Laboratory criteria:

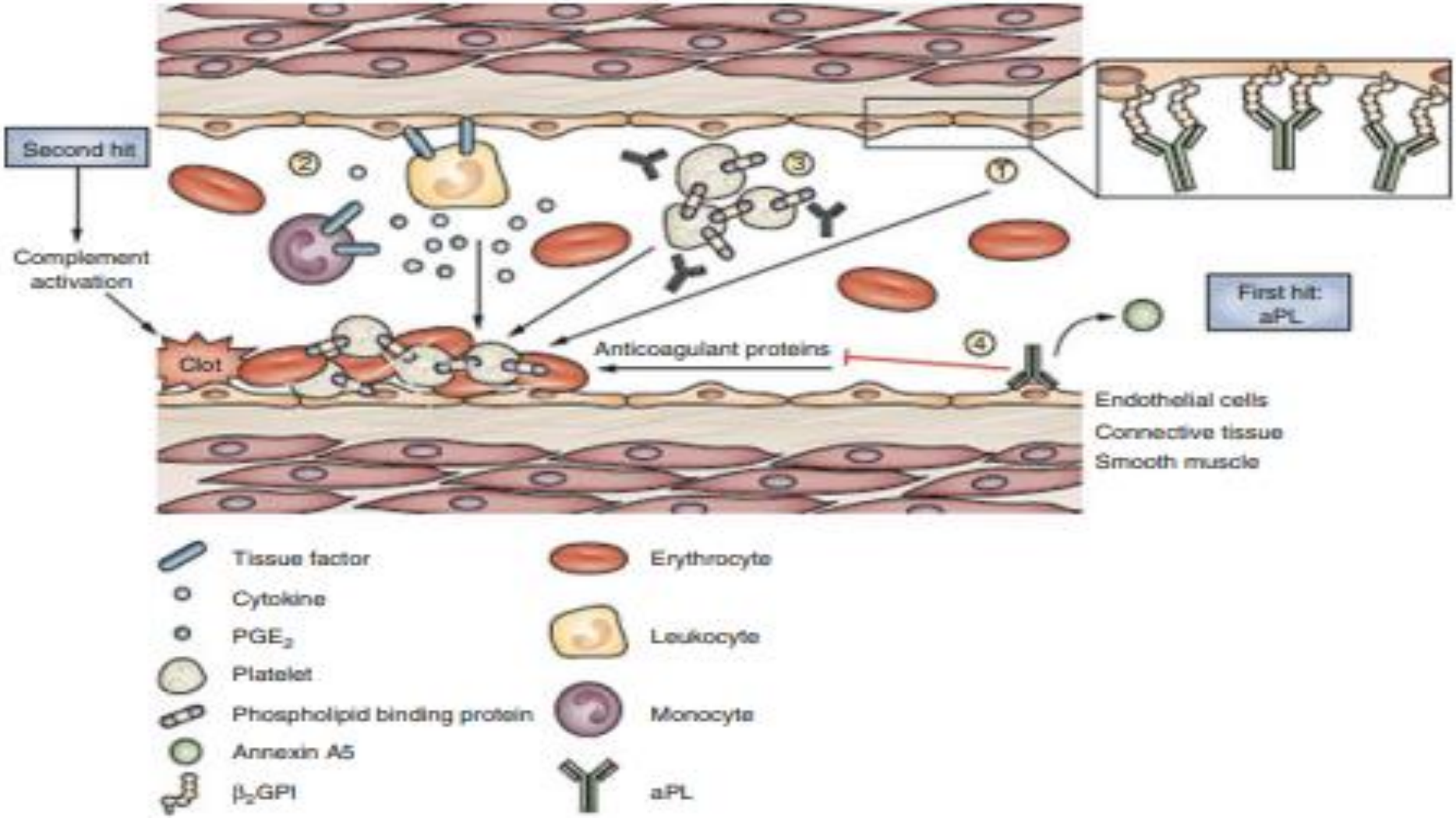
Any must be present on two or more occasions at least 12 weeks apart:

- LA present in plasma, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
- IgG and/or IgM isotype aCL present in medium to high titre (i.e. >40 IgG phospholipid units or IgM phospholipid units) as measured by standard ELISA
- IgG and/or IgM isotype anti-β2GP1 antibody in serum or plasma, present in medium/high titre (e.g. >99th centile)

To fit the classification, one feature from each set of the clinical and laboratory criteria is required. The classification criteria are primarily a research tool, and do not include all clinical features or manifestations. See text for abbreviations.

S. MIYAKIS et al. J. Thromb Haemost, 2006

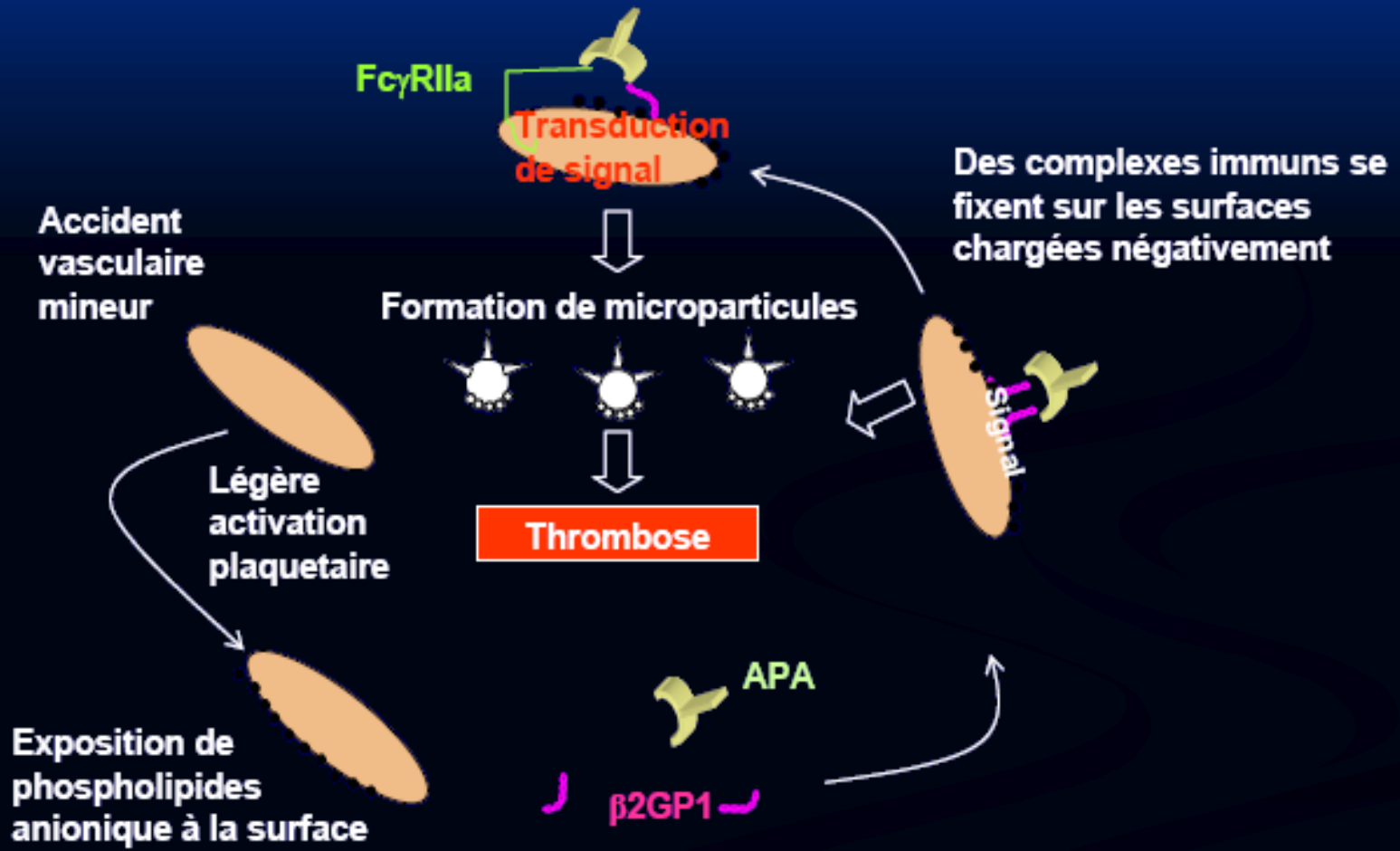
Mécanismes physiopathologiques



from Meroni et al

SAPL/Physiopathologie:

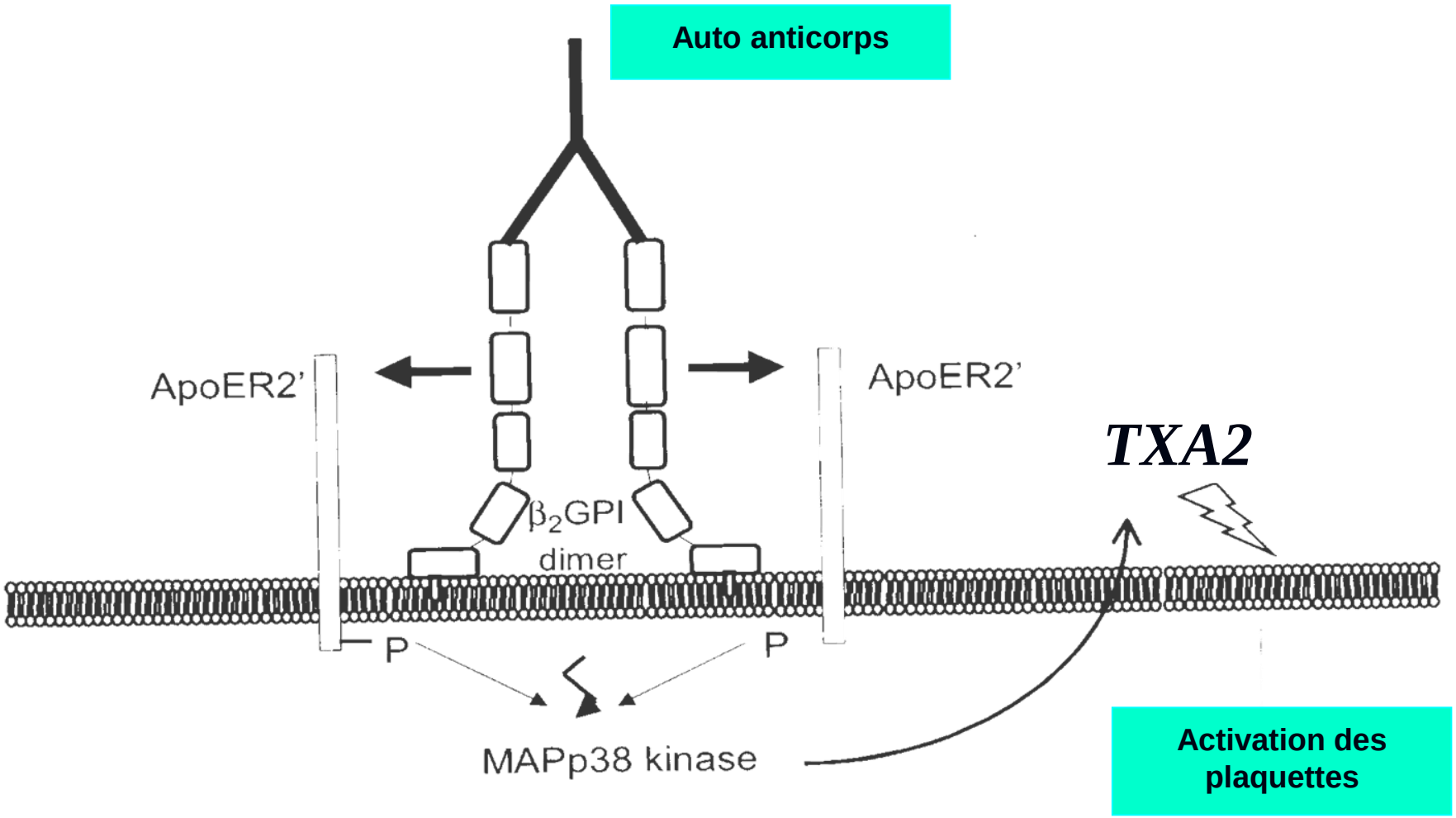
Anomalie des fonctions plaquettaires



D'après Arnout et al. Leuven 2003

SAPL/Physiopathologie

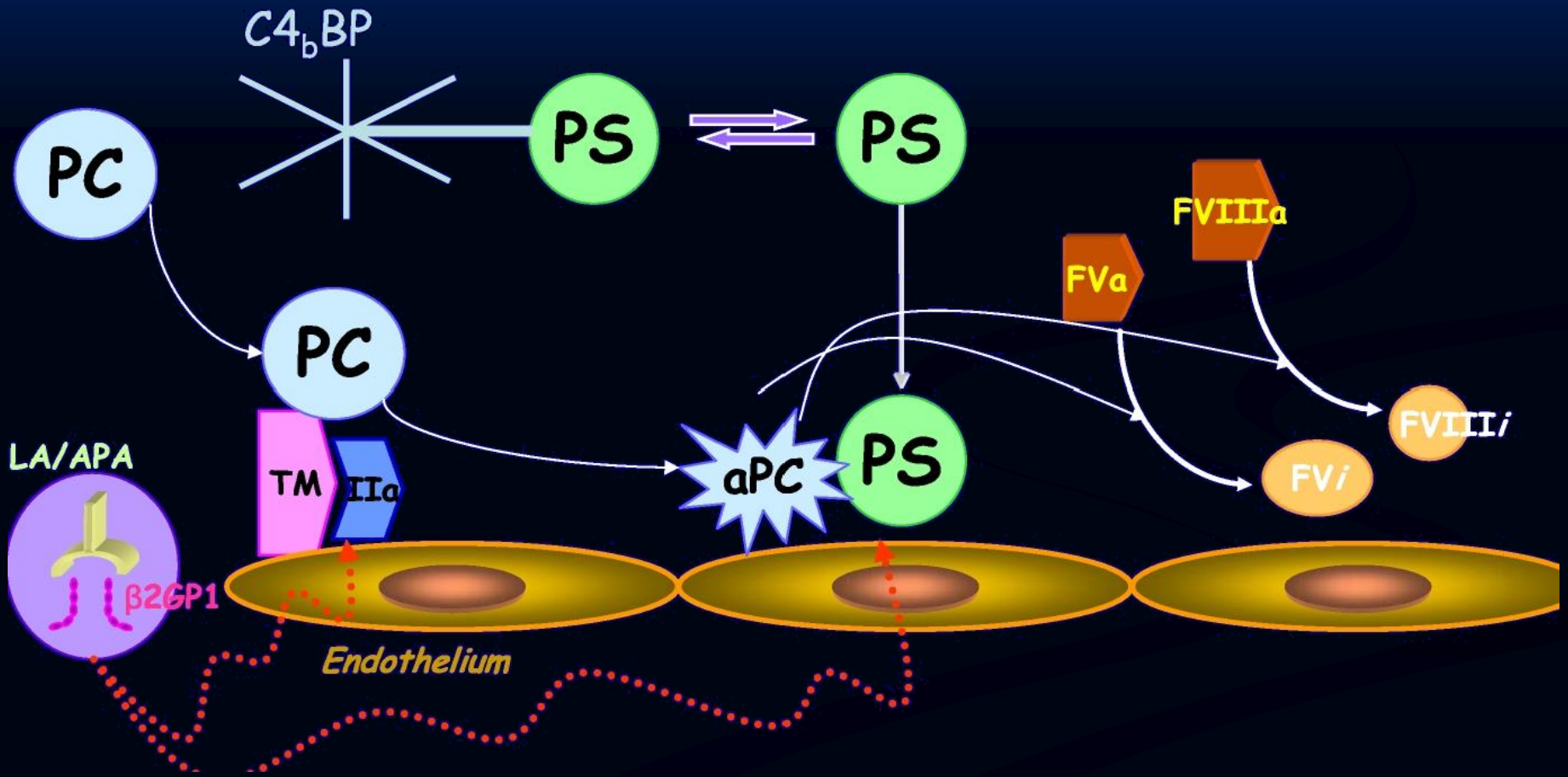
Activations cellulaires



D'après De Groot 2005

SAPL / Physiopathologie

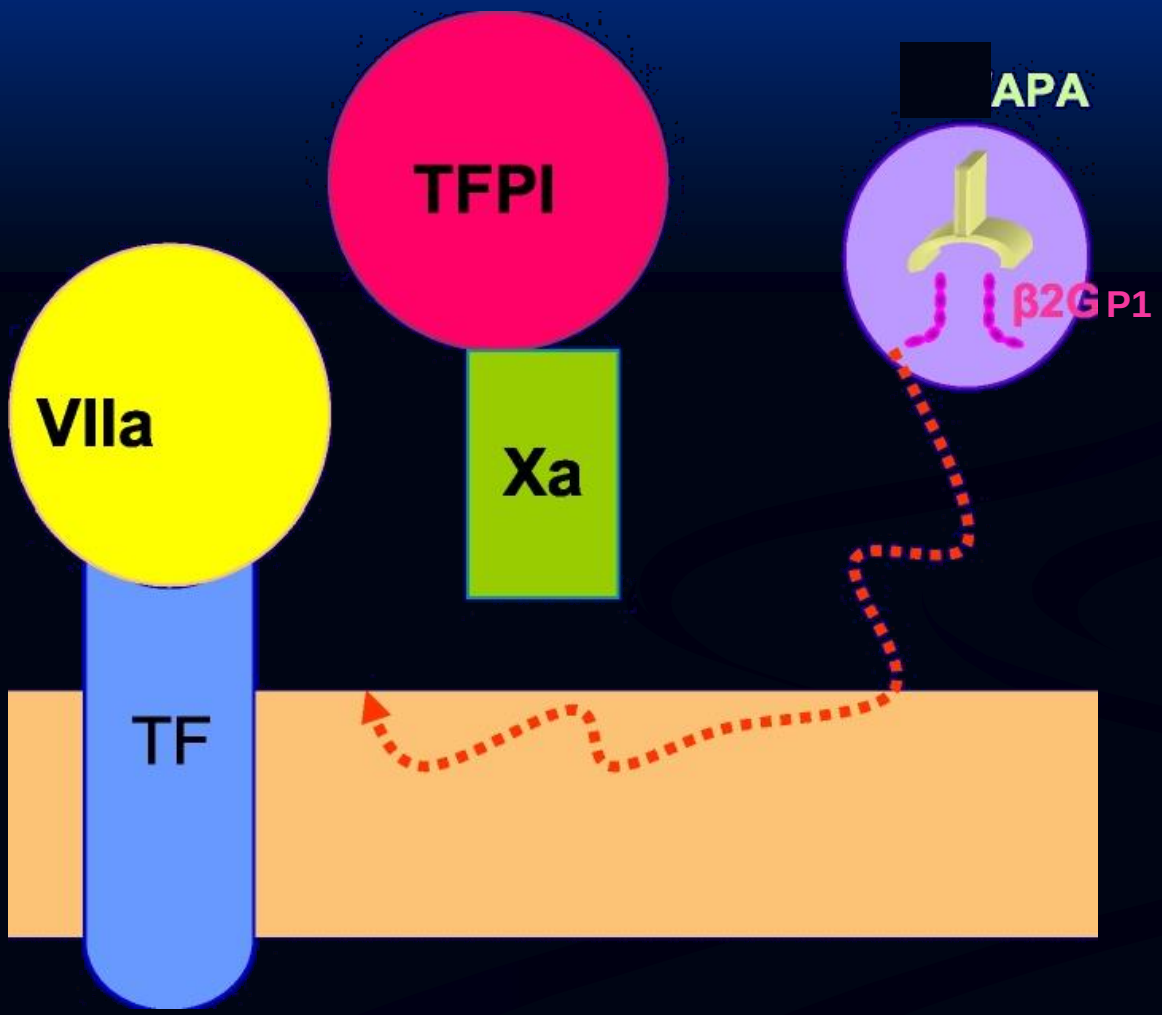
Inhibition de la voie de la protéine C activée



D'après Makxorth-young et col 2004

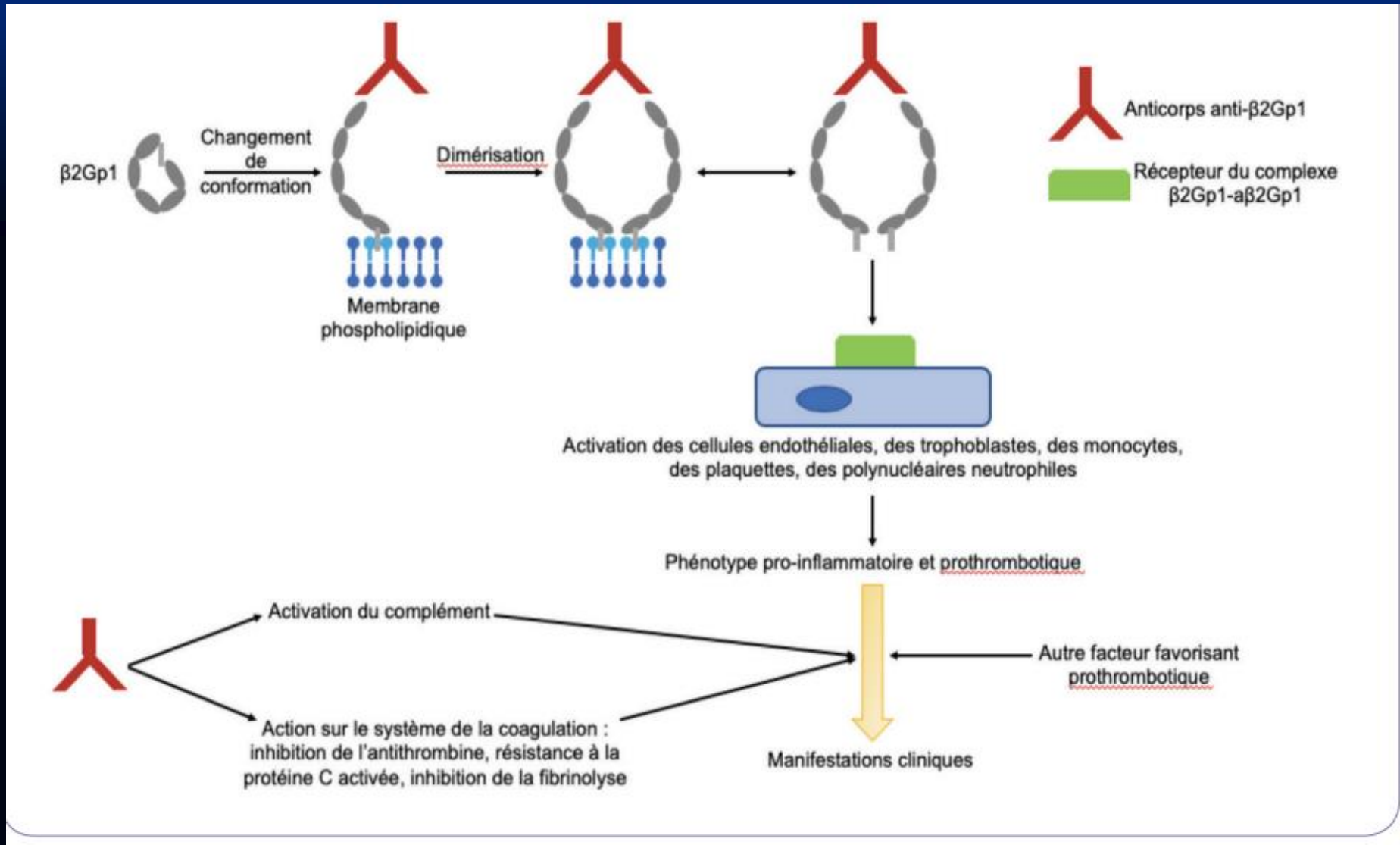
SAPL / Physiopathologie

Stimulation de la voie du facteur tissulaire

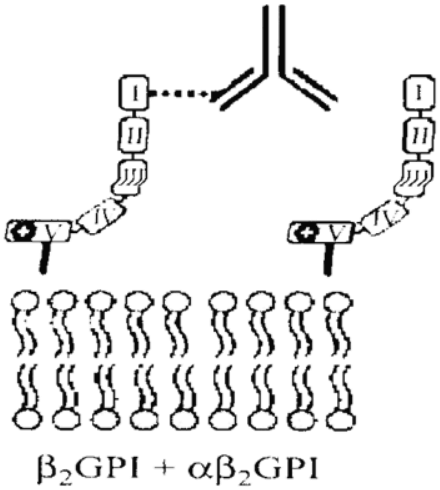


D'après *Wolberger A.S. et al. 2004*

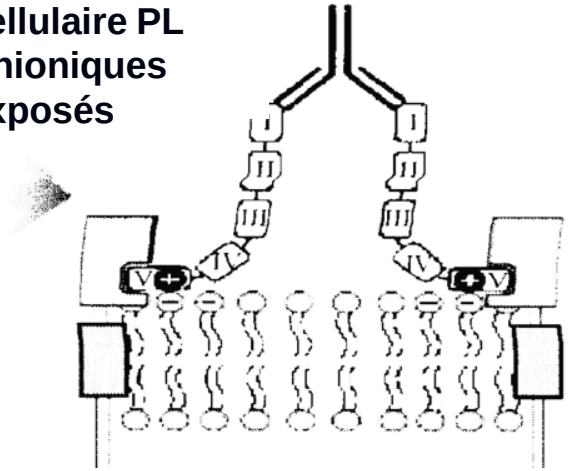
Mécanismes impliqués dans les manifestations cliniques du SAPL



aβ2GPI

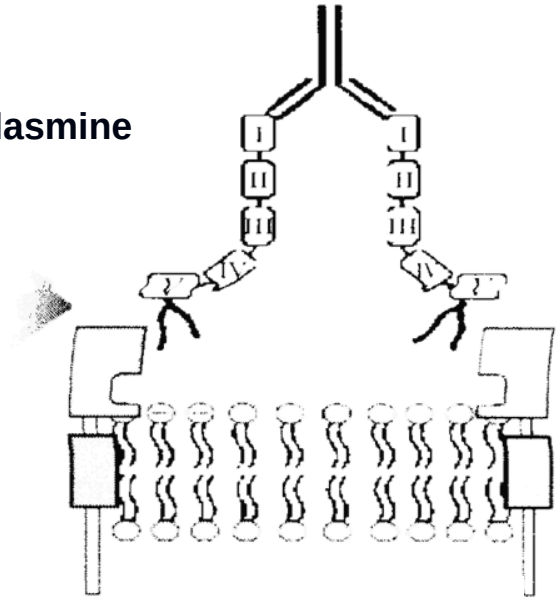


Activation cellulaire PL Anioniques exposés



Dimérisation de la β2GPI liaison au récepteur ApoER2 et signal cellulaire

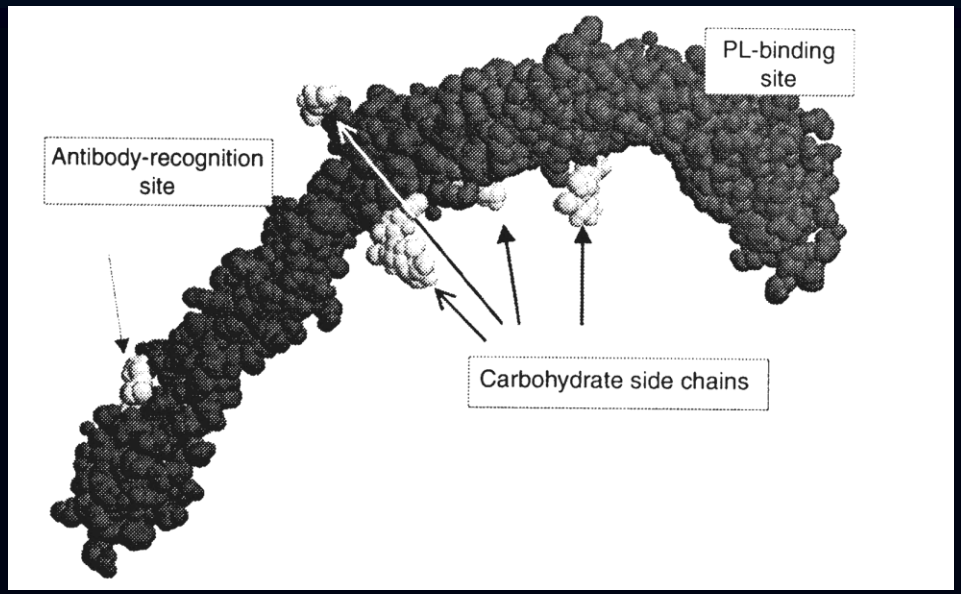
Plasmine

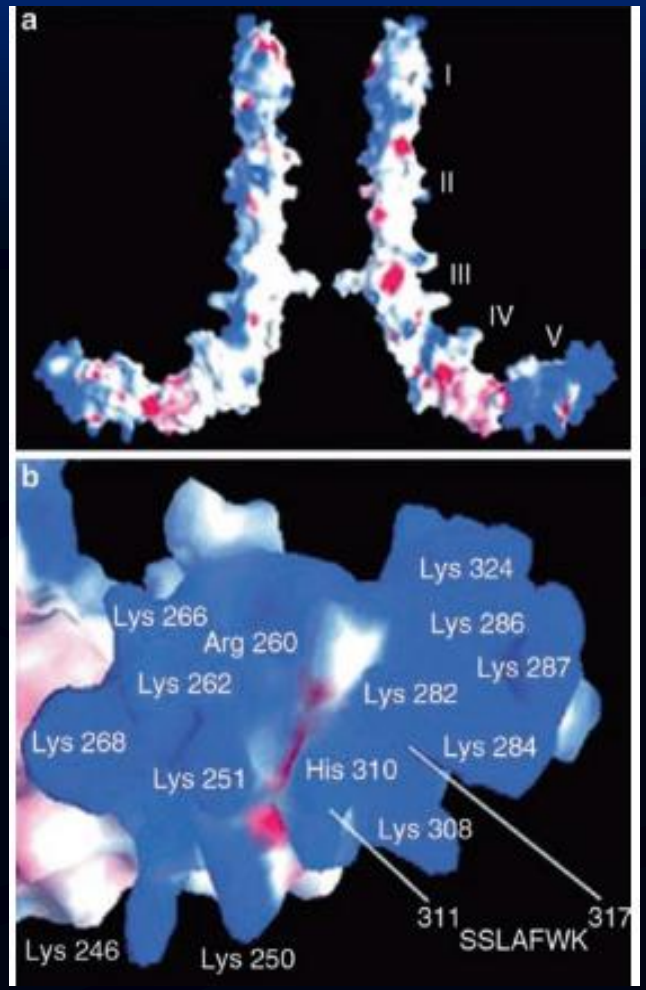


Clivage dissociation de la β2GPI,

D'après De Groot 2005

antiβ2GPI antibodies with DI specificity

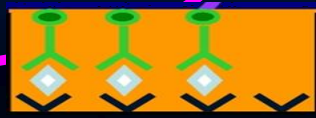




spécificités des aPL

Lupus Anticoagulants (LA)

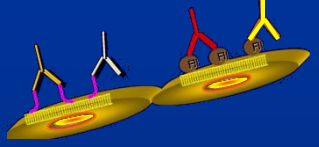
Anticorps Antiphospholipides (aPA)



Tests de coagulation Phospholipide dépendant

ELISA (aPA/β2GPI)

- **Principales protéines cibles : β2GP1 -prothrombine**
- **Critères biologiques / SAPL (aPA/LA)**
- **Taux de recouvrement LA /aCL 60%**

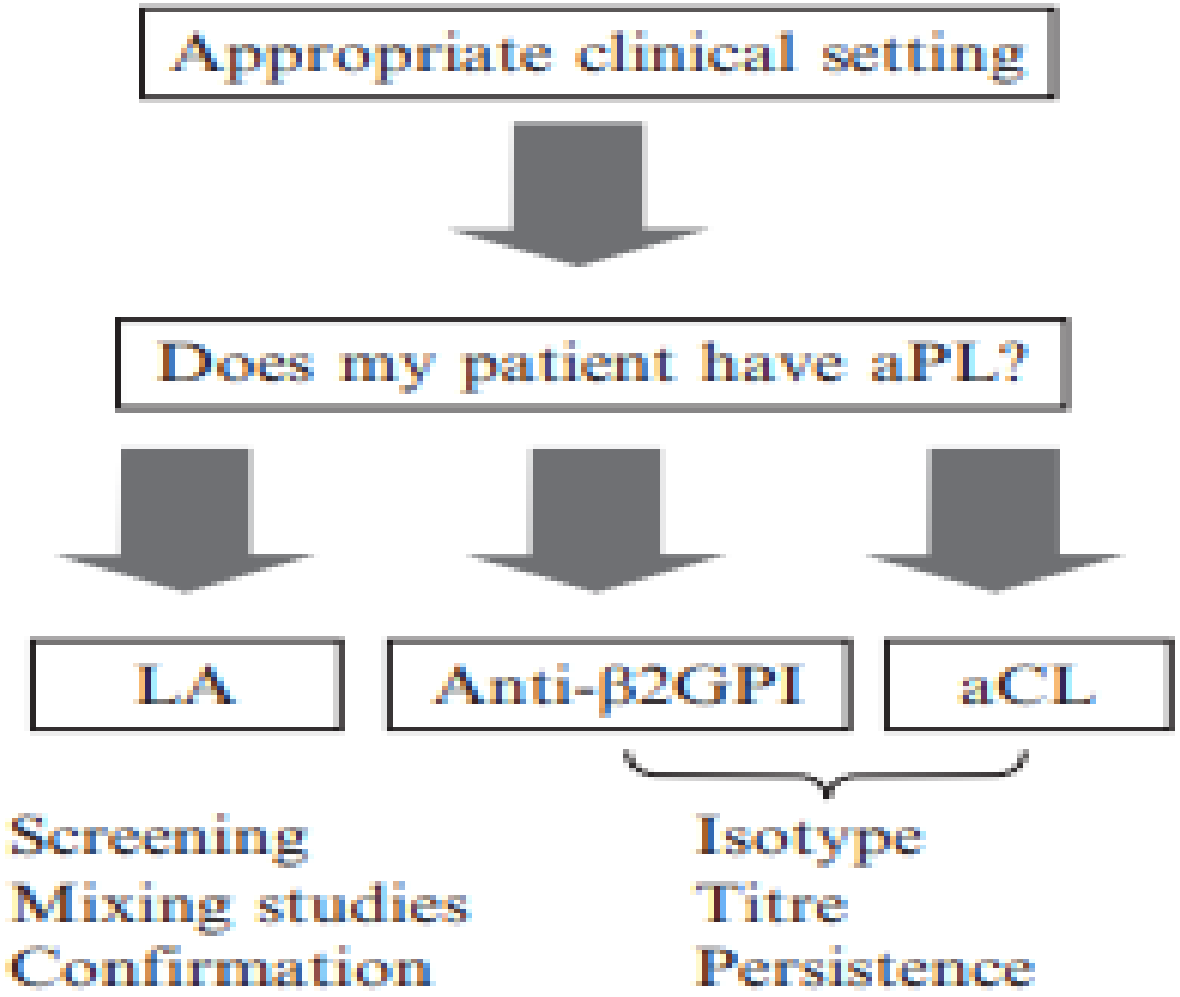


AUTRES TYPES D'ANTICORPS

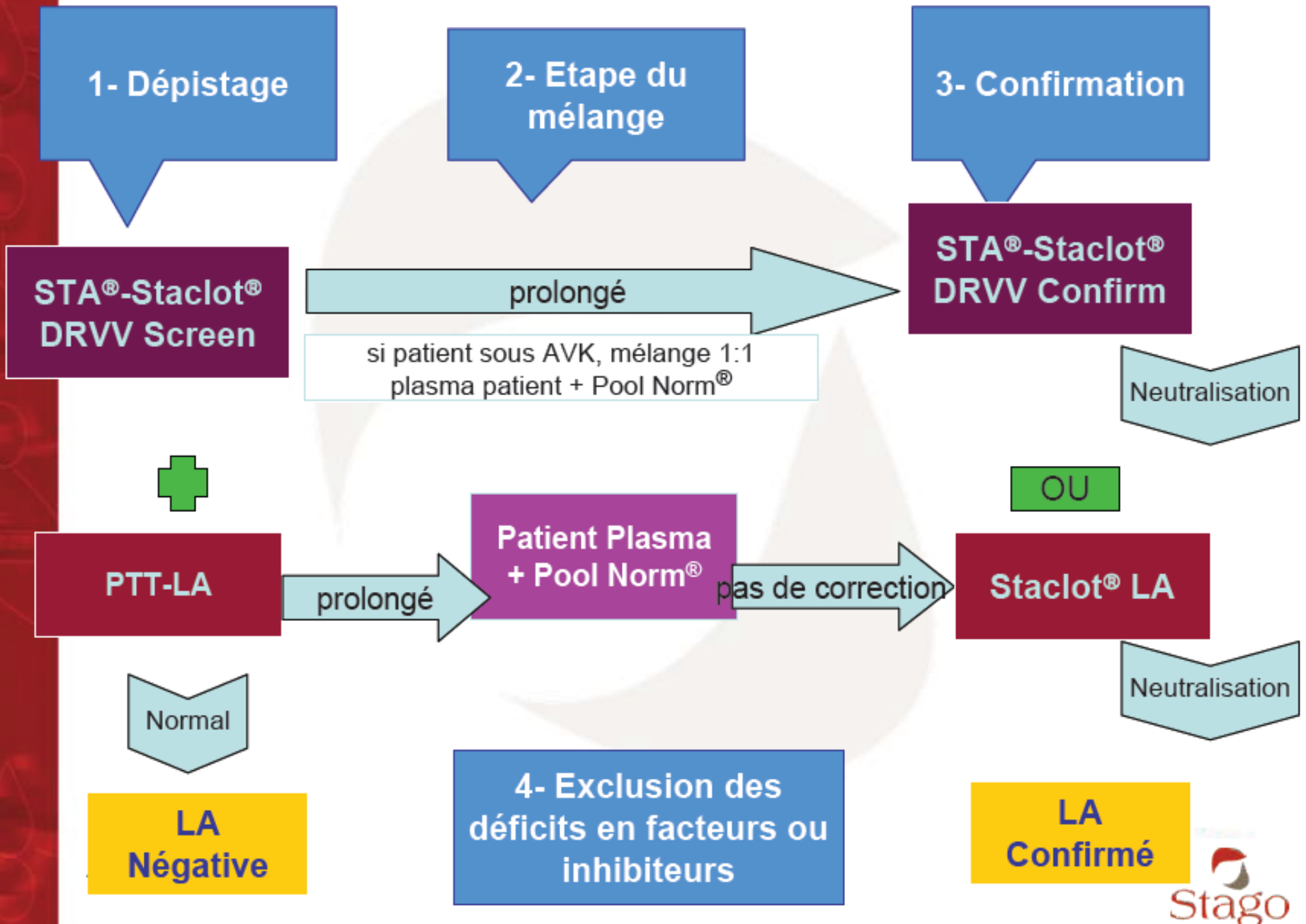
Test	Distinctive features
Anti-PS/PT antibodies	Strong correlation with LA
	Association with obstetric or thrombotic manifestations not definitely demonstrated
Anti-DI antibodies	Association with triple positivity
	Association with thrombosis (in few studies)
	Controversial data in OAPS
Anti-PE antibodies	No association with additional aPL laboratory tests
	Proposed as a possible serological marker of seronegative APS
Ab against negatively charged PLs[a]	aCL cross-react with aPS, aPA, and aPI
	Mainly recognize β2GPI complexed with anionic aPL
	Conflicting data regarding association with pregnancy morbidity
Annexin A5 resistance assay	Association with anti-DI
	Found in a significantly higher proportion of APS patients in comparison to controls
Anti-annexin 2	Described in patients with APS and severe thrombosis and/or pregnancy morbidity
IgA aCL and/or IgA anti-β2GPI	Reported in seronegative patients with a history of thrombosis and pregnancy morbidity

[a]Ab against negatively charged PLs: anti-phosphatidylserine (aPS), anti-phosphatidylinositol (aPI), and anti-phosphatidic acid (aPA)

DIAGNOSTIC/ALGORITHME SAPL

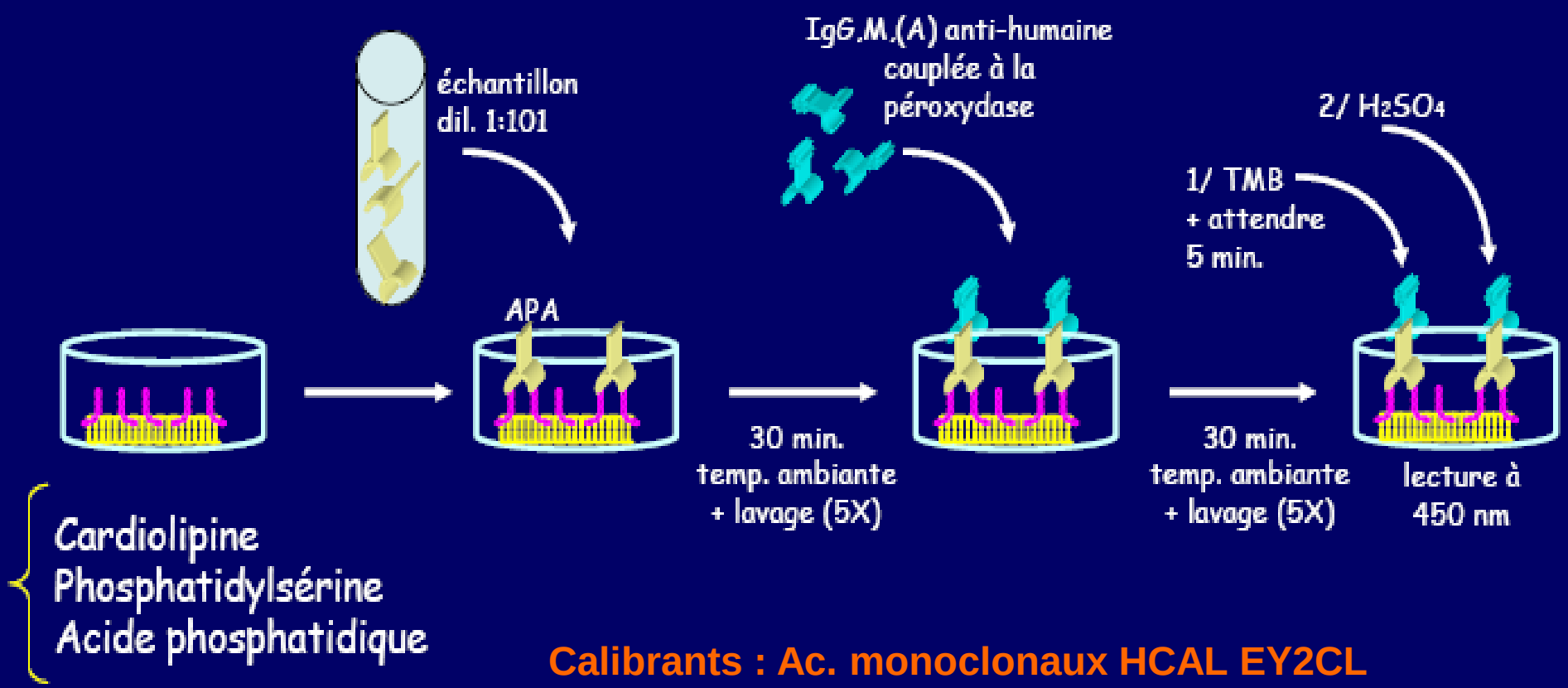


Suggestion d'algorithme pour la détection des LA



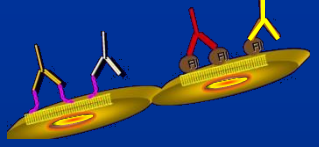
Techniques immunologiques (ELISA)

aPA/ β2GPI IgG - IgM



Calibrants : Ac. monoclonaux HCAL EY2CL

Anticorps anti-cardiolipine (titre>40 GPL ou MPL)



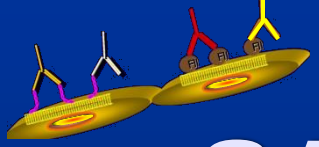
EPIDEMIOLOGIE

APL

- Prévalence : 1 et 5 % /PG .
- APL transitoires +++ sans traduction clinique.
- souvent rencontrés en cas d'infections ,de vaccinations et de pathologies tumorales. traitements,
- APL persistants /SAPL

SAPL

- pathologie rare.
- Incidence: 5 nouveaux cas / an pour 100 000 p
- prévalence : 40 à 50 cas / 100 000 p.
- Pathologie féminine ++++ 1H/5F
- âge moyen au diagnostic de 42 ans

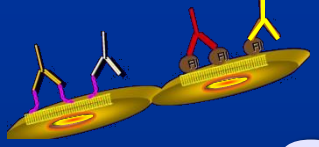


SAPL/Risque thrombotique

- 30 % à 40 % des patients avec des APL présentent des manifestations thrombotiques

- Des scores cliniques, comme le GAPSS peu utilisés en pratique clinique

- Selon Devresse et al., le risque de thrombose semble être plus faible chez les femmes présentant un SAPL avec des manifestations exclusivement obstétricales .



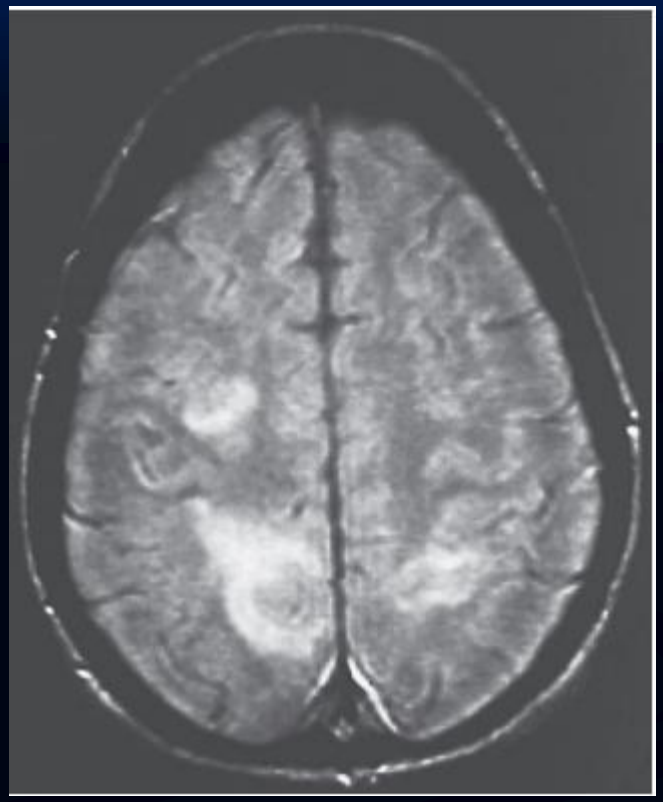
SAPL/Risque thrombose

- La découverte d'APL /bilan /patient asymptomatique /pas d'augmentation significative du risque thrombotique
- le risque thrombotique /type APL détectés.
- le risque de thrombose était multiplié par 5 en cas de LA positif et par environ 3 en cas d'aCL positif /cohorte patients avec ou sans LED.

CLINIQUE/SAPL

Manifestations neuropsychiatriques

- Cerebrovascular disease:
  - Stroke
  - TIA
  - Cerebral venous sinus thrombosis
  - Acute ischemic encephalopathy
- Chorea
- Atypical migrainous-like events
- Seizures
- Headache
- Multiple sclerosis-like syndrome
- Idiopathic intracranial hypertension
- Transverse myelopathy
- Other neurological syndromes:
  - Sensorineural hearing loss (sudden or progressive)
  - Guillain-Barré Syndrome
  - Transient global amnesia
  - Ocular syndromes (Amaurosis fugax, ischemic optic neuropathy, vaso-occlusive retinopathy)
  - Dystonia-Parkinsonism
  - Progressive supra-nuclear palsy
  - Diabetic peripheral neuropathy
  - Orthostatic hypotension
- Cognitive dysfunction
- Dementia
- Psychiatric disorders (depression, psychosis)



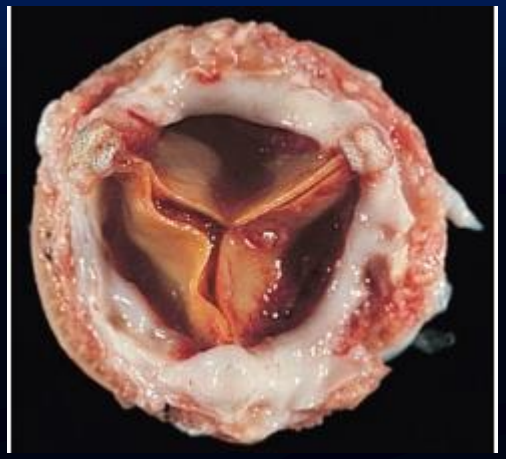
IRM / multiple strokes in a young woman with APL, strokes, and seizures, from Khamashta 2000

SAPL/Manifestations cardiaques

Valves:
- Leaflet thickening (the most frequent)
- Vegetations (Libman-Sacks endocarditis)
- Stenosis
- Regurgitation

Coronary arteries:
- Ischemic heart disease: Myocardial Infarction, Angina, Cardiac Syndrome X.
- Coronary bypass graft and angioplasty occlusions.

Other:
- Intracardiac thrombus
- Acute/chronic cardiomyopathy (due to microangiopathy)



Valvular thickening and thrombosis in a prosthetic mitral valve of a patient. With primary APS, from Khamashta 2000

Manifestations cutanées

Livedo reticularis

Ulcers

Necrotizing vasculitis

Livedoid vasculitis

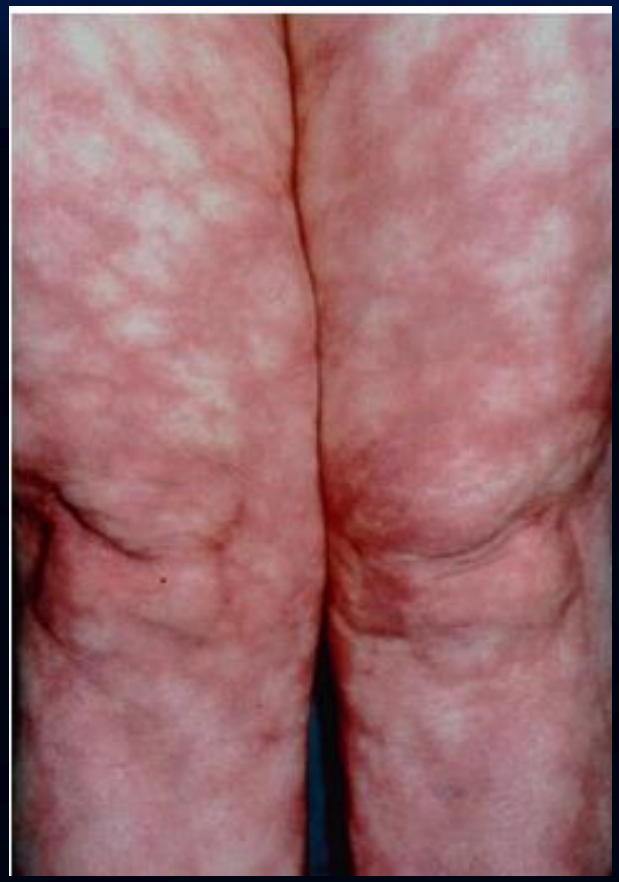
Cutaneous gangrene

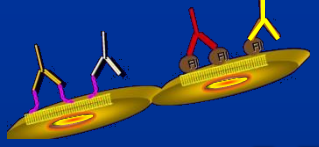
Superficial thromphlebitis

Pseudovasculitis lesions: nodules, papules, pustules, palmar-plantar erythema

Splinter hemorrhage

Anetoderma



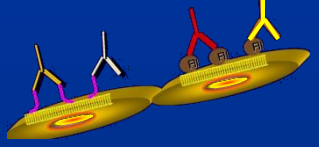


Manifestations hématologiques

Thrombocytopénie autoimmune
Anémie hémolytique autoimmune
Anémie hémolytique microangiopathie
Purpura thrombocytopénique et thrombotique

Manifestations obstétricales

- *Miscarriages (before 10 weeks)*
- *Fetal death (after 10 weeks) Pre-eclampsia, eclampsia, and HELLP syndrome Placental insufficiency (prematurity, fetal growth restriction) Abruption*



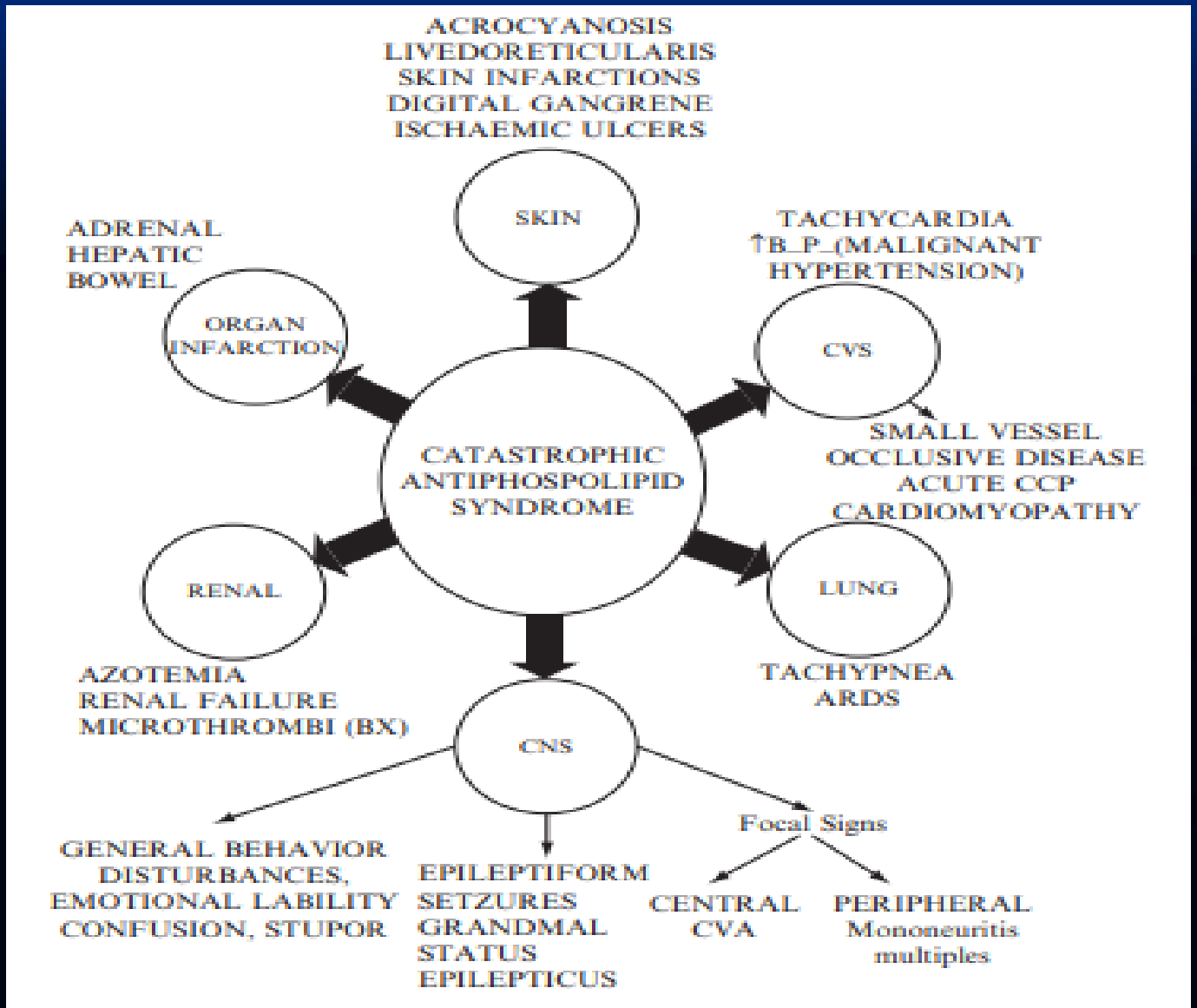
SAPL PRIMAIRE/SECONDAIRE

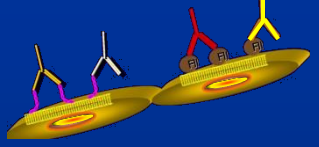
Patients with primary APS (PAPS) have no other autoimmune conditions.

secondary APS (SAPS) is diagnosed where the criteria for APS are ful filled in the presence of another condition – most commonly systemic lupus erythematosus (SLE) .

The catastrophic APS (CAPS), a dramatic variant of APS, is characterized by acute widespread coagulopathy affecting small vessels leading to rapid multi-organ failure with high mortality rate .

Manifestations of CAP

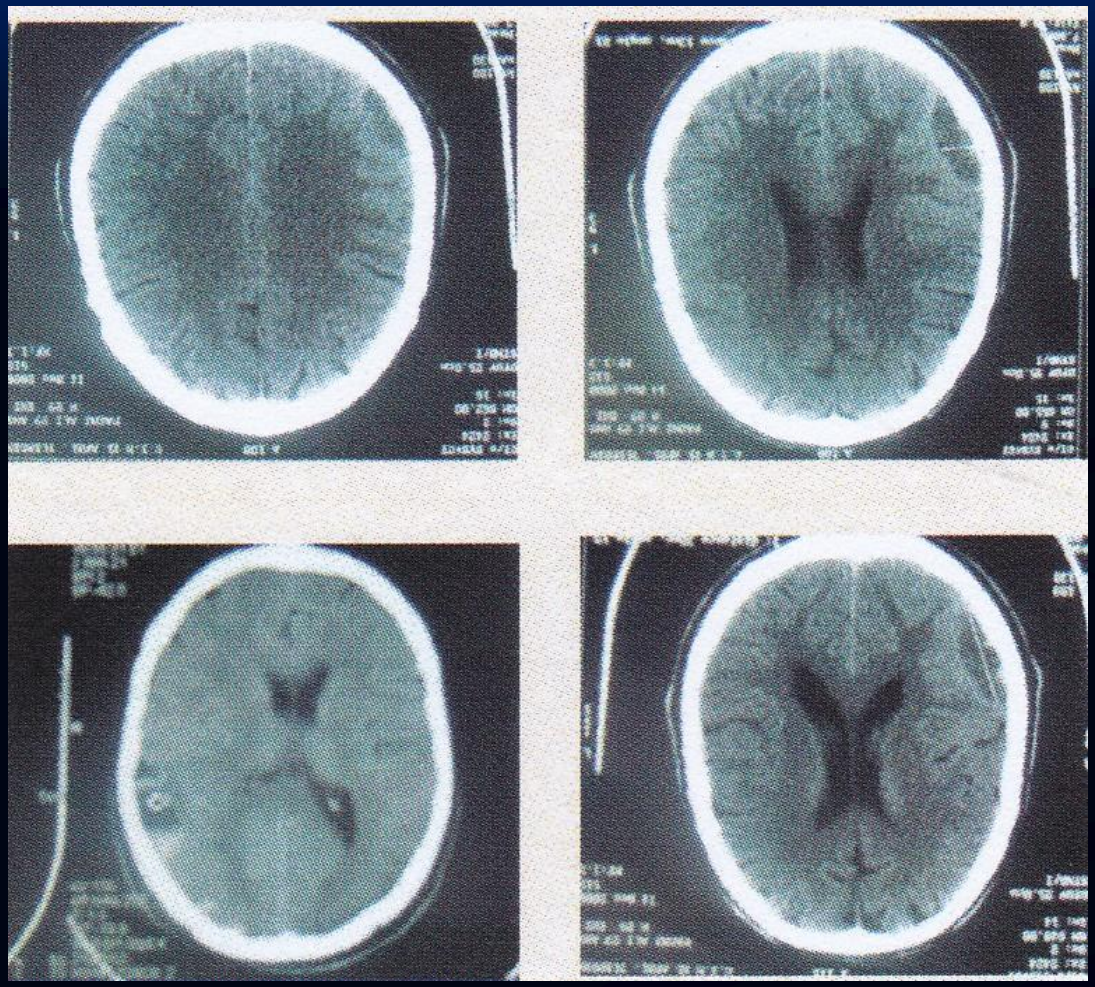


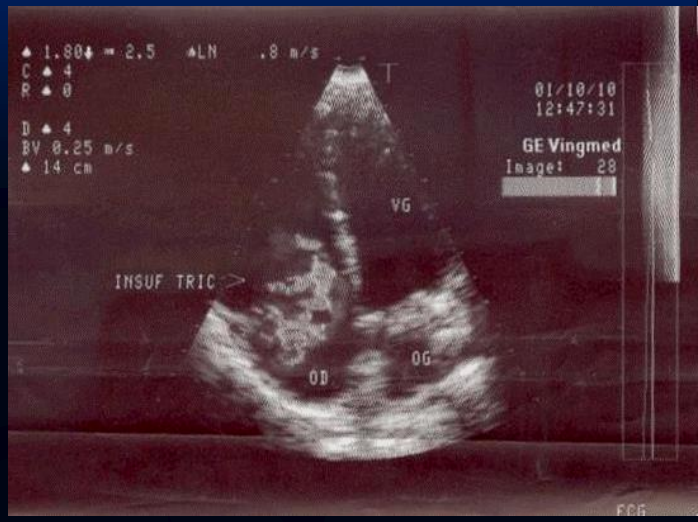


Critères CAPS

1. Evidence of involvement of 3 organs, systems, and/or tissues
2. Development of manifestations simultaneously or in less than 1 week
3. Laboratory confirmation of the presence of aPL (LAC and/or aCL and/or anti-2GPI antibodies) in titers higher than 40 UI/l
4. Exclude other diagnosis
Definite CAPS:
All 4 criteria
Probable CAPS:
All 4 criteria, except for involvement of only 2 organs, system, and/or tissues
All 4 criteria, except for the absence of laboratory confirmation at least 12 weeks apart associable to the early death of a patient never tested for aPL before onset of CAPS
1, 2, and 4
1, 3, and 4 and the development of a third event in >1 week but <1 month, despite anticoagulation treatment

Observations particulières

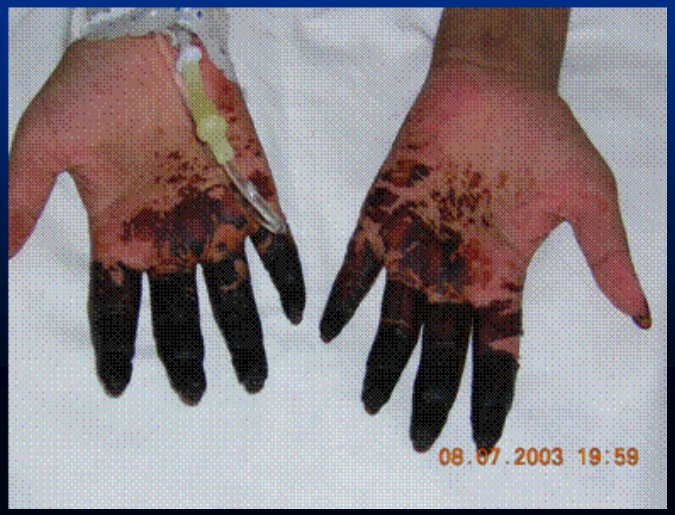


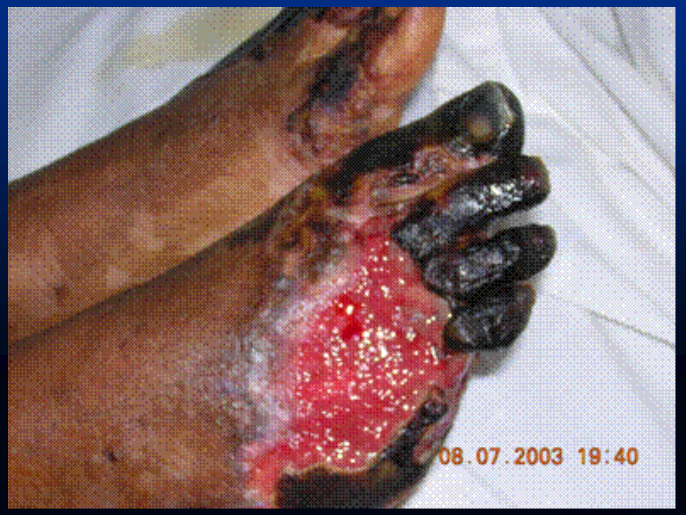


42 ANS /LED 9 abrt a mort in utero/TV MI Thrombose intracardiaque et endocardite de Liebmann sachs

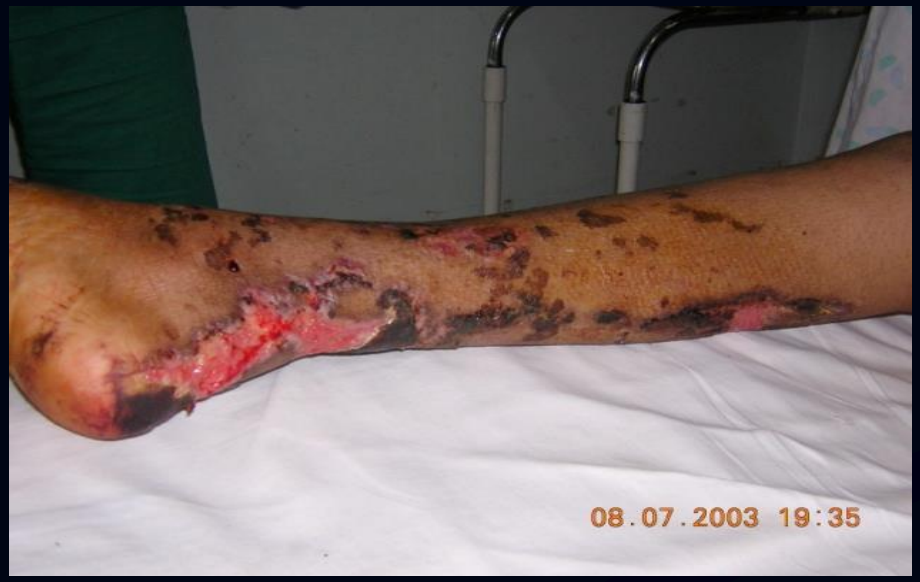
Triple positif

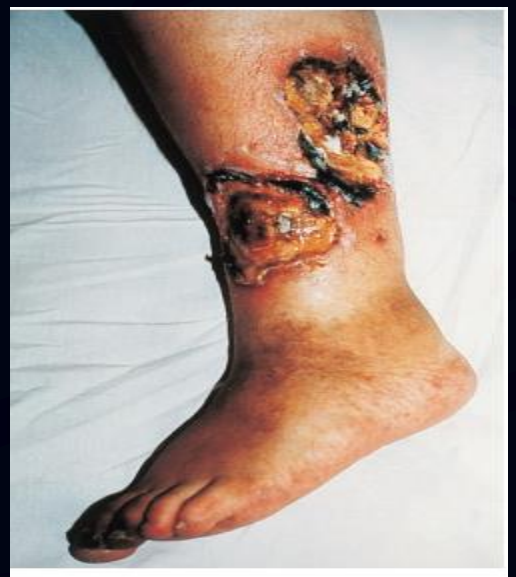
Observations particulières





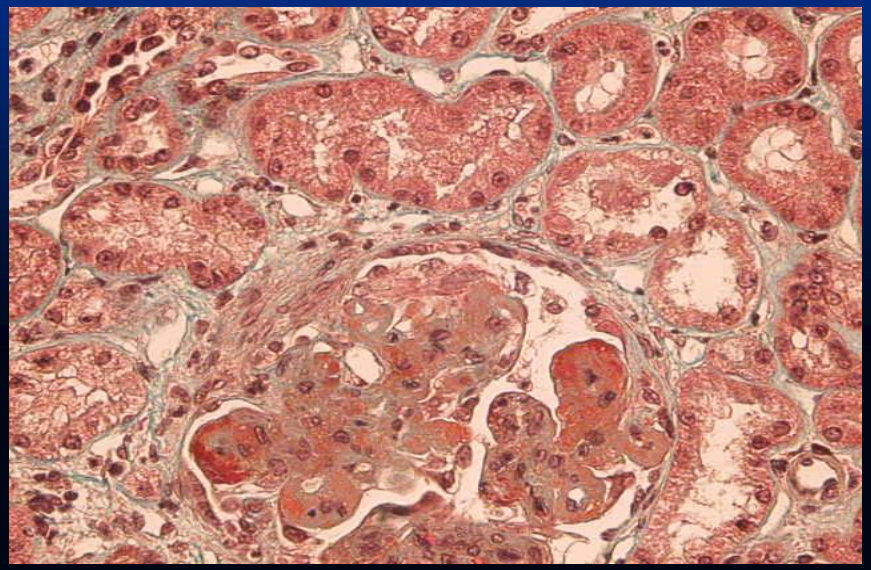
Catastrophic antiphospholipid syndrome



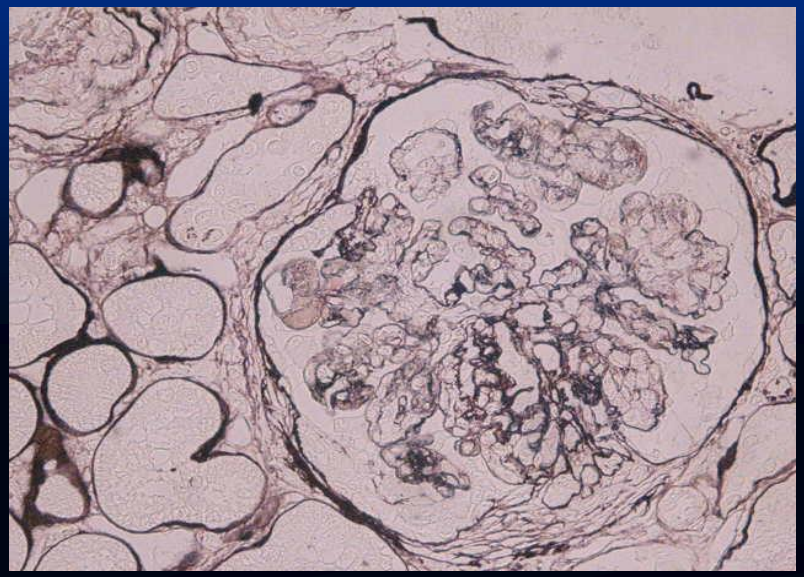


Patient with primary APS that presents necrotic ulcers on the leg and necrosis of the toes, from Khamashta 2000

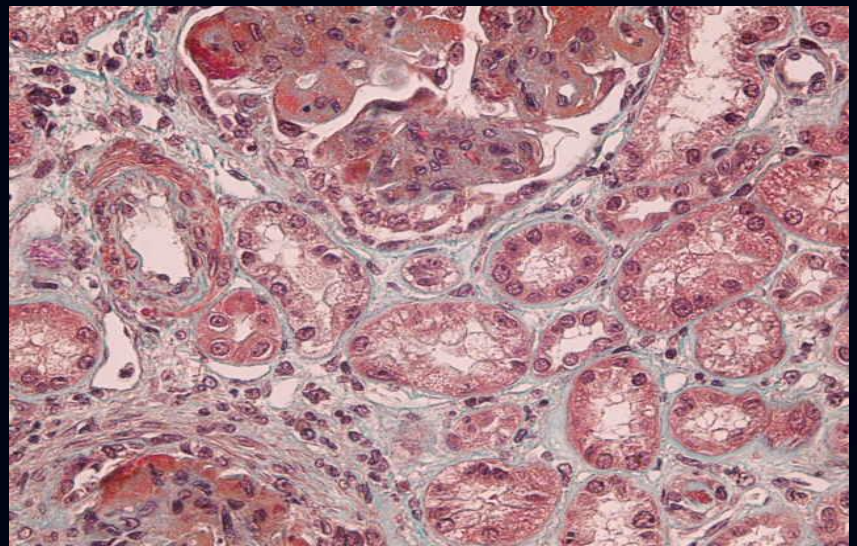
Observation particulière/Renal arterial thrombosis SAPL/LES/Triple positif

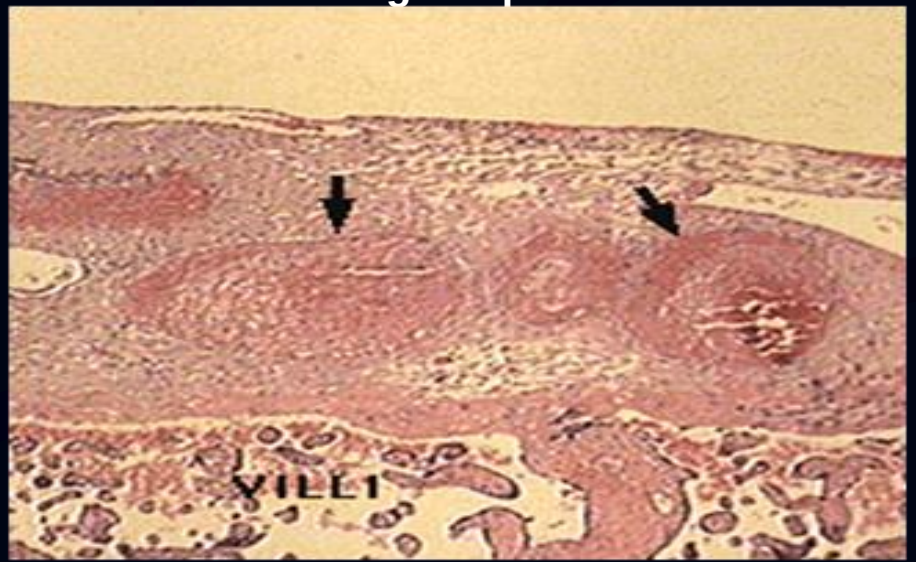


Thrombi capillaires glomérulaires obstructifs

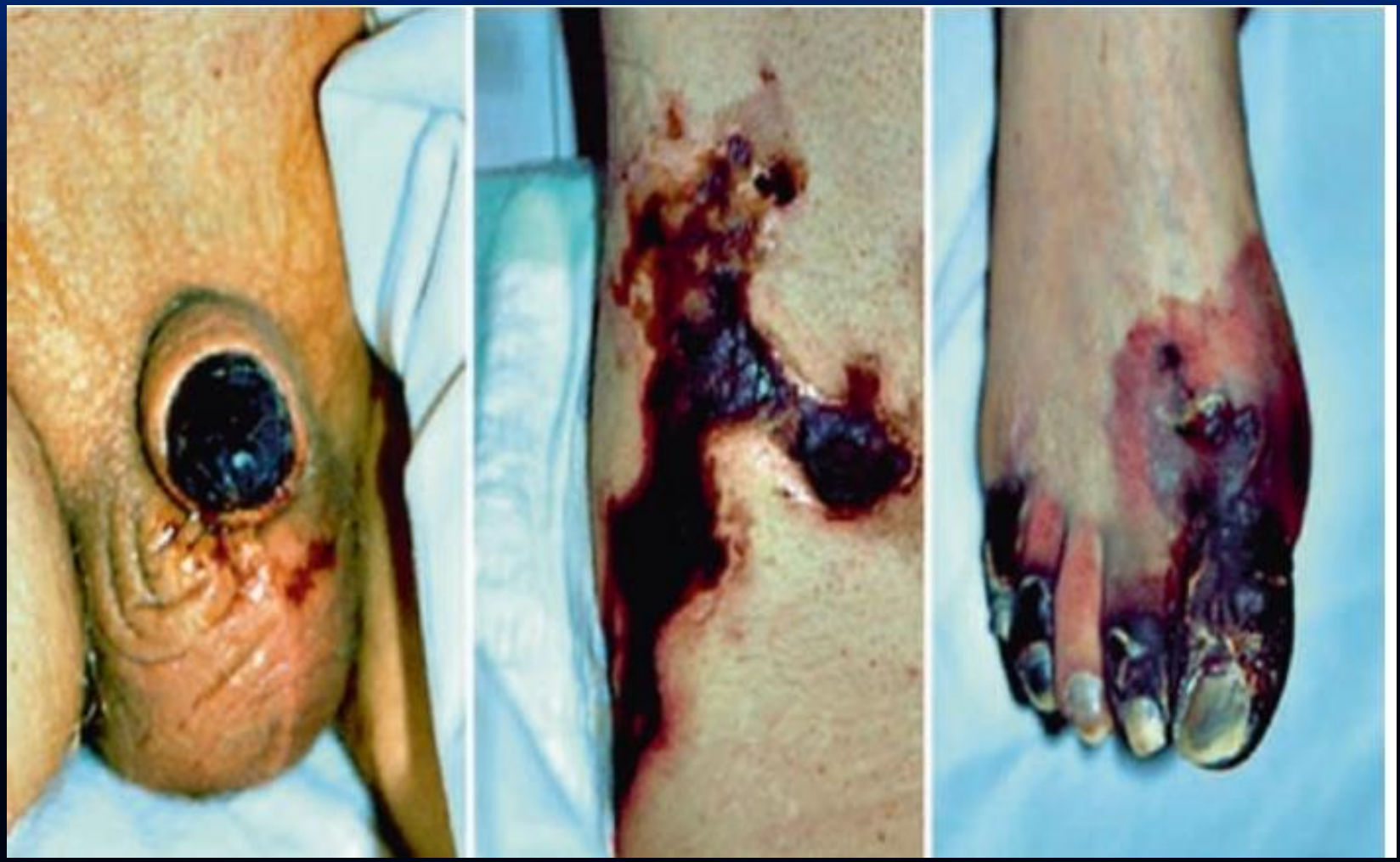


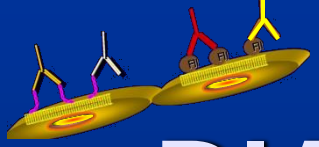
Coloration argentique doubles contours





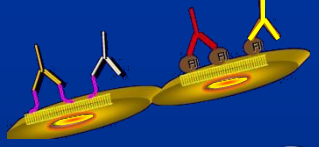
CAPS





DIAGNOSTIC DIFFERENTIEL

- *RPCA /factor V Leiden*
- *Déficits en : Antithrombin/ Prot-C / Prot-S/ Prothrombin 20210*
- *Myeloproliferative disorders and Malignancies (Trousseau's syndrome)*
- *Syndrome nephrotique*
- *Syndrome de Behçet - Dysfibrinogenemie – Thrombopénie induite par l'héparine - Hyperhomocysteinemie –HPN*
- *Disseminated intravascular coagulation (DIC) Hyperviscosity syndromes Sneddon's syndrome, Susac's syndrome, Degos disease, Moyamoya syndrome (very rare) a TTP thrombotic thrombocytopenic purpura, HUS hemolytic uremic syndrome….*



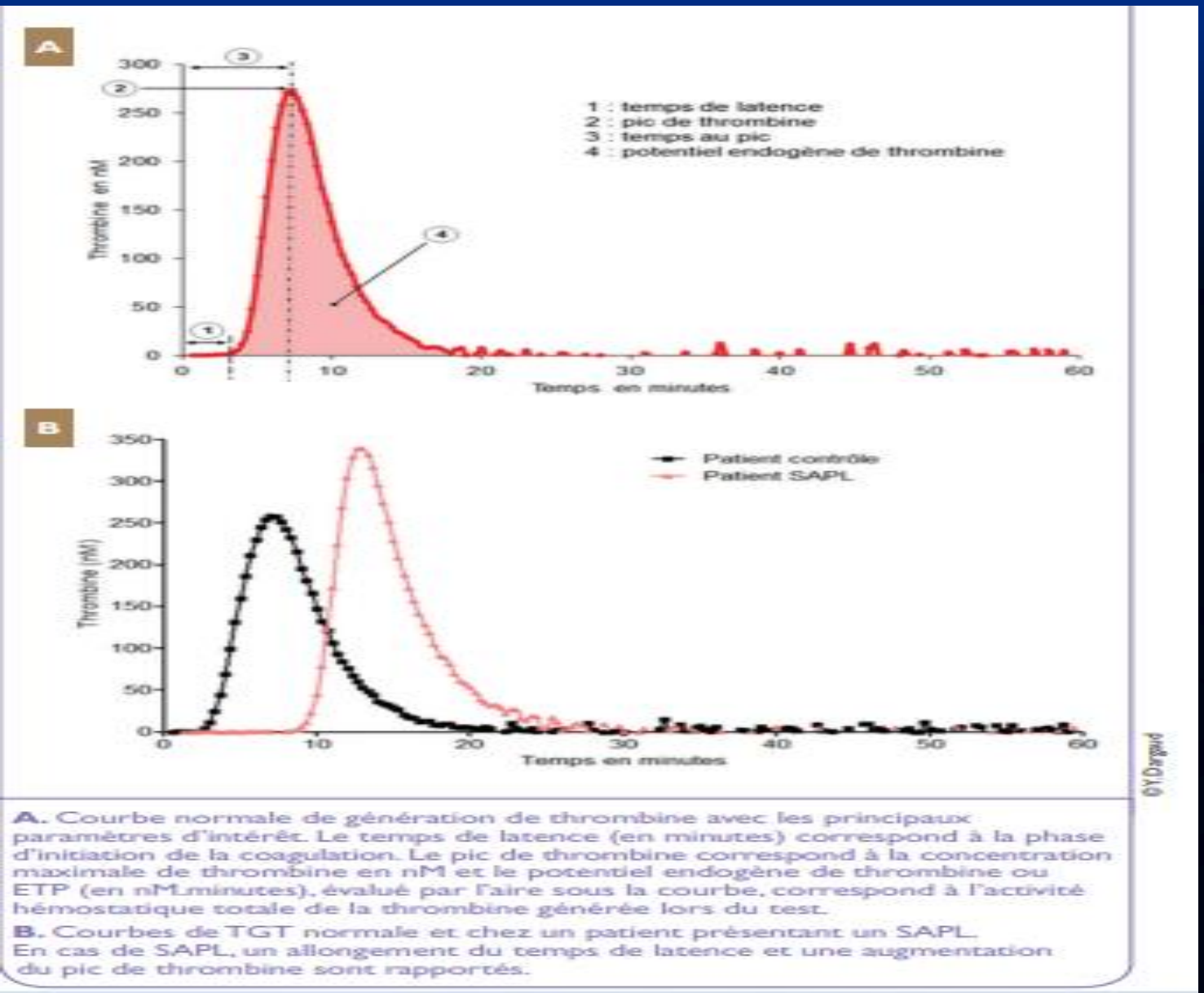
SAPL et recidive thrombotique

- *nature des APL/ risque de récidive thrombotique / multiplié par 11 en cas de LA + et par 4 en cas d'aCL positif chez des patients atteints d'un lupus .*

- *nombre de tests biologiques positifs / risque accru chez les patients avec un **profil biologique triple positif** comparé à ceux ayant un profil double ou simple positif .*

- *incidence cumulée à un an des évènements thrombo emboliques veineux était de 12 % environ chez des patients avec un profil triple positif*

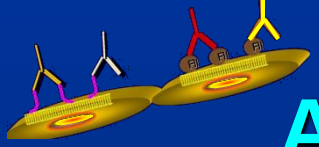
Autres tests biologiques en développement pour une meilleure prédiction du risque thrombotique clinique



A. Courbe normale de génération de thrombine avec les principaux paramètres d'intérêt. Le temps de latence (en minutes) correspond à la phase d'initiation de la coagulation. Le pic de thrombine correspond à la concentration maximale de thrombine en nM et le potentiel endogène de thrombine ou ETP (en nM.minutes), évalué par l'aire sous la courbe, correspond à l'activité hémostatique totale de la thrombine générée lors du test.

B. Courbes de TGT normale et chez un patient présentant un SAPL. En cas de SAPL, un allongement du temps de latence et une augmentation du pic de thrombine sont rapportés.

Le test de génération de thrombine



Anticorps antidomaine 1 de la β2-Glycoprotéine 1

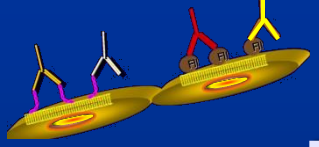
- *test de détection automatisé disponible ; des aβ2Gp1-dm1*

- *+profil biologique triple positif / valeur moyenne significativement plus élevée par rapport aux patients « double positif » et « simple positif » .*

- *aβ2Gp1-dm1 / antécédents thromboemboliques et obstétricaux des patients*

- *À l'inverse, pour certains auteurs, il n'y a pas de valeur ajoutée à la détection des aβ2Gp1-dm1 dans le diagnostic du SAPL*

d'autres études semblent nécessaires pour préciser la place des aβ2Gp1-dm1 dans le diagnostic du SAPL et la prédiction du risque thromboembolique



TRAITEMENT DU SAPL

1. *APL+: aspirine long terme (et LMWH situations à risque)*
2. *SAPL*

   (a) aPL positive +

   thromb veineuse (ATCO INR 2.0–3.0)

   – TA ou V severe (INR 3.0–4.0)

   – Throm recurrentes (INR 3.0–4.0) (b)

   Manif obstétricales sans throm: *aspirine long terme (et LMWH situations à risque)*

AUTRES TRAITEMENTS

Hydroxychloroquine /risque thrombotique et LES.

Drogues immunosupressives

Corticosteroides /rare/SAPL Obstétrical/thrombopénie

RITUXIMAB/SAPL Résistant/CAPS

AVK et Aspirine/TA
Evaluer risque hémorragique

Statines, Hydroxychlo/HBPM

Autres traitements

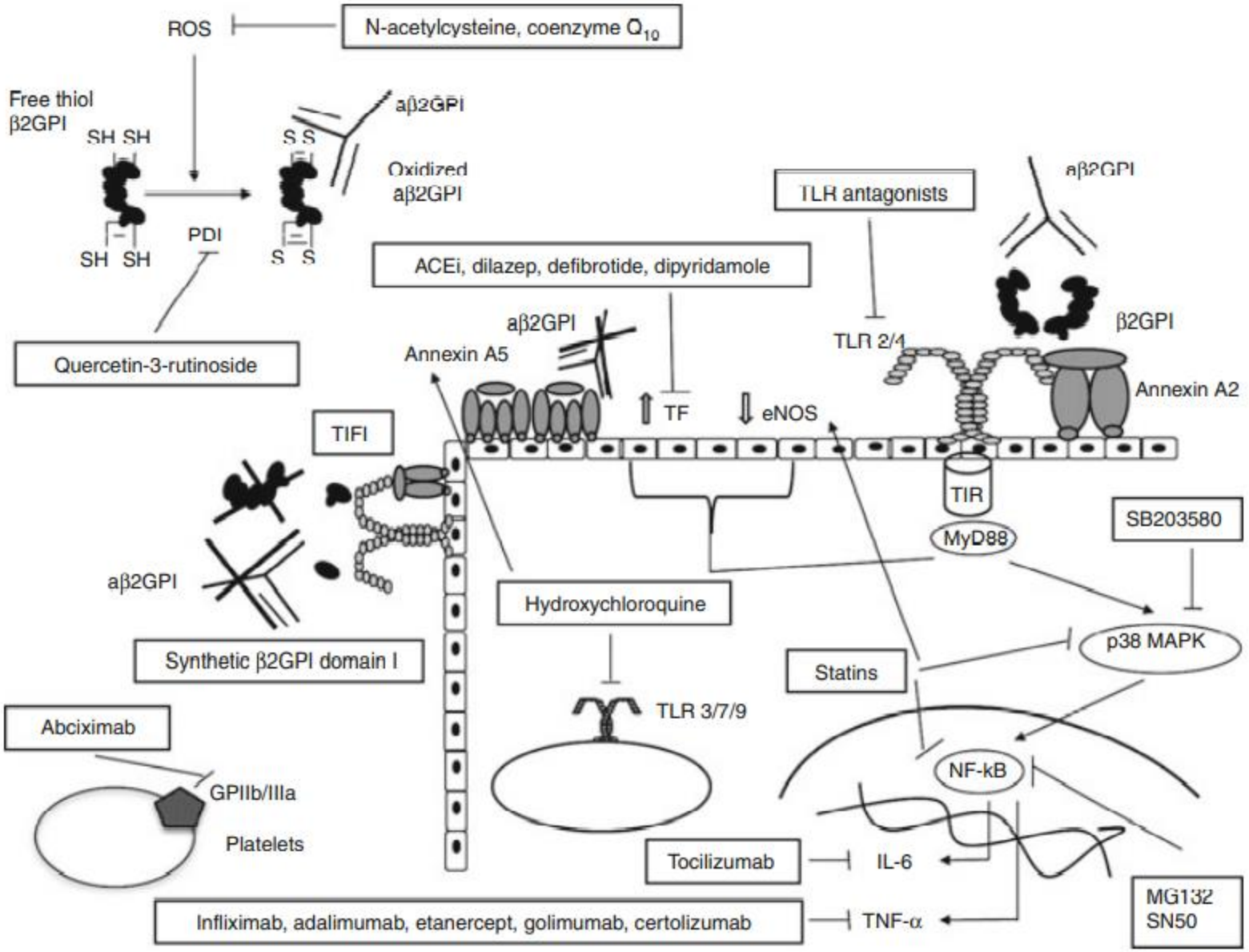
Nouveaux médicaments anticoagulants oraux (NOA)

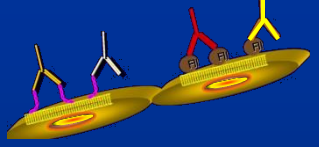
- *Difficulté de gérer /Trt AVK*
- *Prévention de la TEV/*
- *Chirurgie orthopédique élective*
  AVC et embolie systémique
- *Fibrillation auriculaire*

Dabigatran et exilate (Anti IIa)
rivaroxaban et de l'apixaban (Anti Xa)

FDA
EMA

Mécanisme d'action des molécules thérapeutiques



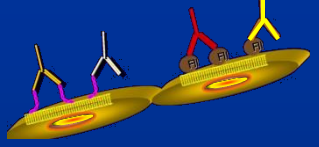


Alternative and future potential therapies and diagnostic assays in APS

Potential adjunctive therapies	
Statins	Some benefit in recurrent TE despite anticoagulation. Potential adjunctive therapy
Eculizumab	C5 inhibitor. Case reports of its use in preventing APS-associated thrombotic microangiopathy after renal transplantation, as well as recurrent CAPS
Sirolimus	Blocks B and T cell activation by inhibiting mTOR. No recurrence of APS nephropathy in renal transplant patients being given sirolimus, and decreased vascular proliferation
Autologous stem cell transplant	Promising early studies in SLE and APS, but high rates of adverse events
Belilumab	Two case reports in primary APS improving recurrent pulmonary necrotizing neutrophilic capillaritis, and skin ulceration
Novel therapies in development	
NFkB and p38 MAPK inhibitors	Effective in reducing the *in vitro* proinflammatory/prothrombotic effect of APS and reduced tissue factor expression
Recombinant DI	Inhibit development of anti-β2GPI antibodies and inhibits aPL-mediated prothrombotic effects in animal models
A1–A1	Dimeric inhibitor selectively targets β2GPI in β2GPI–antibody complexes, interfering with *in vitro* interaction with anionic phospholipids and ApoER2

ApoER2, apolipoprotein E receptor 2; MAPK, mitogen-activated protein kinase; NFkB, nuclear factor κB; TE, thromboembolism; TF, tissue factor.

Kristina EN Clark Ian Giles 2021 Published



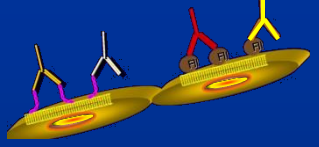
CONCLUSION

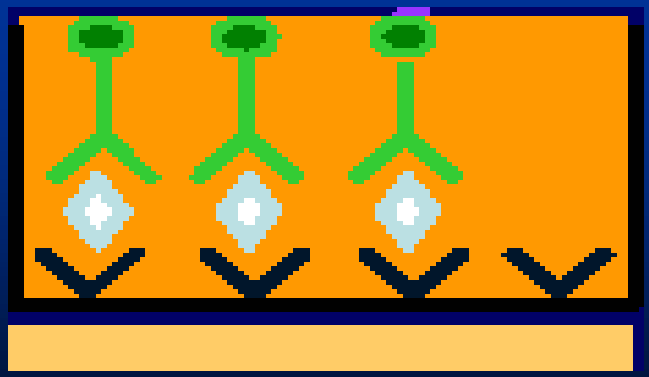
Bilan biologique SAPL : LA,aCL et Ac anti- β2Gp1 /Clinique +++ bilan devant être contrôlé à ***douze semaines*** *lorsqu'il est positif/5ans*

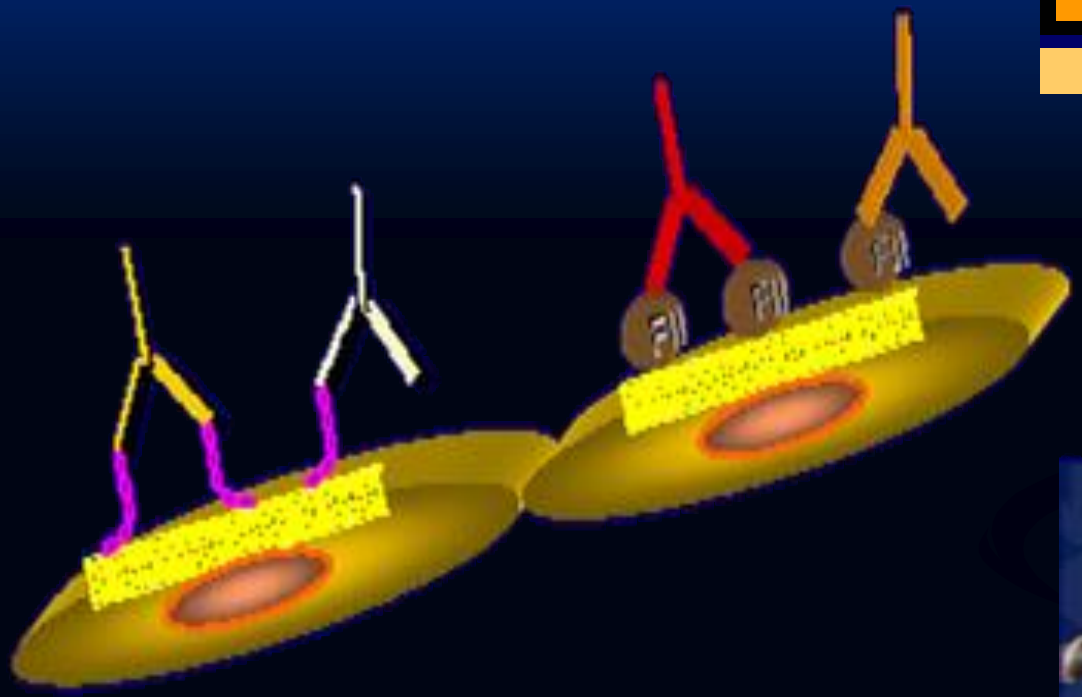
À l'heure actuelle, l'enjeu principal de cette pathologie demeure la prédiction du risque de manifestations cliniques.*

Il a été récemment montré que les patients « triple positif » sont ceux présentant le risque thrombotique le plus élevé.

D'autres tests biologiques, comme ***le test de génération de thrombine ou la recherche d'anticorps anti-domaine 1 de la β2Gp1, semblent être prometteurs pour prédire le risque thrombotique.***







Merci de votre attention