Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

POST- ASH MEETING

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PLATELETS AND COAGULATION

- **I. Thrombosis**
  - IA. New anti-aggregant drugs
  - IB. New anticoagulant drugs

- **II. Hemostasis**
  - Gene therapy : viral vector → production of clotting factor
  - Identification of agents that increase expression or stimulate release of coagulation proteins
  - Emerging non peptide molecules that affect hemostasis
  - Bio-engineering strategies to modify hemostatic proteins

IA. New anti-aggregant drugs

- **elinogrel**
- **vorapaxar**
- **atopaxar**
- **rutin**

elinogrel

- **Mechanism of action**
  - reversible inhibition of P2Y12 receptor
- **Structure**
  - quinazoline-2,4-dione
- **Route of administration**
  - oral and intravenous
- **Stage of development**
  - fase II trial = INNOVATE-PCI → fase III trial starting

PAR (protease activated receptor) antagonist

- **Thrombin is a potent activator of human platelets via action on two platelet surface G-protein coupled receptors PAR 1 and PAR 4**

- **PAR 1- and PAR 4-antagonists are therefore inhibitors of thrombin-induced platelet activation; but they do <u>not</u> affect thrombine-induced cleavage of fibrinogen**

SCH 530348 = vorapaxar

- **Mechanism of action**
  - reversible PAR1 inhibition
- **Structure**
  - tricyclic 3-phenylpiridine analog of himbacine
- **Route of administration**
  - per os
- **Stage of development**
  - fase III trial (TRA-CER, TRA 2P-TIMI 50 : stop 1 of 3 arms due to excessive intracranial hemorrhage in patients with history of ischemic stroke) // Ticocci et al, NEJM 23 nov 2011

E5555 = atopaxar

- **Mechanism of action**
  - reversible PAR1 inhibition
- **Structure**
  - 2-iminopyrrolidine antagonist
- **Route of administration**
  - per os
- **Stage of development**
  - fase II trial

rutin

- **Mechanism of action**
  - reversible PAR4 inhibition
- **Structure**
  - quercetin rutinoside (flavonoid family)
- **Route of administration**
  - po and IV
- **Stage of development**
  - preclinical

IB. New anticoagulant drugs

- **semuloparine**
- **edoxaban**
- **ISIS-FXI**

semuloparine

- **ULMWH = ultra low molecular weight heparin**
- **Anti-Xa activity >> anti-IIa activity**
- **Renal excretion**
- **Subcutaneous administration**
- **Advantages**
  - Half-life = 17 hours (once daily dosing)
  - Rapid onset of action : Cmax reached after 3 hours
- **SAVE-ONCO trial : 1,2% VTE vs. control 3,4 %; but no difference in mortality due to VTE**

edoxaban

- Anti-Xa activity
- Oral administration
- 62% bio-availability
- Rapid onset of action
- Half-life = 8 to 10 hours
- STARS E-III + STARS J-V trial (dubbelblind dubbel-dummy edoxaban 30 mg po versus enoxaparin 2 * 20 mg/d SC) : less VTE, no excess bleeding

ISIS-FXI RX

- Antisense inhibitor of F XI
- Target = mRNA (intranuclear)
- 20 base single strand inhibits transcription and blocks protein production
- Slow onset of action = 14 days
- Half-life = 20 days (dosing every other week)
- No limitation in renal of hepatic failure
- No drug-drug interaction
- Fase II trial

II. Hemostatic drugs

- 1. Gene therapy : viral vector → production of clotting factor
- 2. Identification of agents that increase expression or stimulate release of coagulation proteins
- 3. Emerging non peptide molecules that affect hemostasis
- 4. Bio-engineering strategies to modify hemostatic proteins

1. Gene therapy

- **viral vector = serotype-8-pseudotyped self-complementary adenovirus-associated virus (AAV)**
- **production of codon-optimized factor IX**
- **FU : 6 - 16 months**
- **6 patients with severe hemophilia B**
- **3 cohorts = high, intermediate or low dose viral vector (all without immunosuppressive therapy)**
- **level of factor IX activity 2 to 11%**
- **4 could stop profylaxis and 2 were able to increase interval between injections (still need for clotting factor in case of bleeding and/or surgery)**

Amit C. Nathwani, Edward GD Tuddenham, et al.
NEJM. Dec 2011;365:2357-2365

2. Identification of agents that increase expression or stimulate release of coagulation proteins

- **Interleukin-11**
  - Increases plasma levels of VWF and FVIII
  - Gradual and sustained elevation (opposite to DDAVP)
  - DDAVP releasable pool unaffected
  - Fase II trial using rhIL-11 = Neumega

3. Emerging non peptide molecules that affect hemostasis

- **3.1 Fucoidans (NASP)**
- **3.2 Small molecule-induced read-through of nonsense mutations**

3.1 Fucoidans = NASP (non-anticoagulant-sulfated polysaccharides)

- **Structure**
  - Heterogeneously sized, strongly anionic compounds with a fucose backbone derived from brown seaweed (e.g. AV513)
- **Mechanism of action**
  - Anti TFPI activity
- **Potential strenghts**
  - Oral or subcutaneous administration
  - Reduce dependence on clotting factor concentrate
- **Potential limitations**
  - May exert paradoxal anticoagulant effect at higher doses
- **Stage of development**
  - Preclinical (mice and dogs)

3.2 Small molecule-induced read-through of nonsense mutations

- **Mechanisme of action**
  - Dose dependent read-through of UGA / UAA / UGA nonsense mutation
- **Structure**
  - PTC124 = oxidiazole linked to flurobenzene and benzoic acid ring
- **Potential strenghts**
  - Oral or subcutaneous administration
  - Reduce functional severity of hemophilic phenotype A or B
- **Potential limitations**
  - Only for patients with nonsense mutations (also CF, Duchenne, …)
- **Stage of development**
  - Fase II trial

4. Bio-engineering strategies to modify hemostatic proteins

4.1 Wish list for characteristics of hemophilic treatment

- Least invasive method of administration (TD, po, SC, nasal)
- Least requirement for dose manipulation due to interindividual differences in recovery / clearance
- Maximal (supraphysiologic) half-life
- Lowest or (even better) no immunogenicity
- Highest tolerability
- Lowest thrombogenic risk
- Lowest cost

4.2 Mechanisms

- Chemical modification
  - PEGylation, glycoPEGylation, polysialysation
- Fusion to protein conjugates
  - Fc-IgG fusion, fusion to albumin, fusion to transmucosal carrier protein
- Site-directed mutagenesis : rhFVIIa (NN1731 / BAY86-6150)

PEGylation	-**Prolongs half-life** -**Reduces immunogenicity by shielding epitopes** -**Widely used**	-**Formation of PEG Ab** -**Accumulation of PEG** -**Non targeted conjugation may mask essential functional residues**	-**Fase I : PEG-BDD-rFVIII, glyco-PEG-rFIX** -**Fase II/III : glyco-PEG-rFVIIa**
Polysialysation	-**Length of PAS determines half-life** -**Naturally occurring** -**Non immunogenic**	**- PSA polymers may interfere with enzymatic activity of therapeutic proteins**	**Only animal models : PSA-rFVIII (murine)**

Fc fusion	**-Binding of IgG-Fc fused to therapeutic protein to FcRn in endo-thelial cells** **-Low immuno-genicity of Fc**	**-No shielding of therapeutic protein from neutralizing circulating Ab**	**-Fase II/III : rFVIII-Fc and rFIX-Fc**
Albumin fusion	**-Prolongs t ½**	**-No shielding from immune effector cells**	**-Preclinical : rFVIIa** **-Fase I/II : rFIX**

Fusion to transmucosal carrier protein	**-May reduce inhibitor formation and anafylaxis** **-Bio-encapsu-lation allows oral formula**	**-Hemostatic activity of fused factor protein likely negligible**	**- Animal model only : rFIX**
Site-directed mutagenesis	**-Increased hemostatic activity** **-Decreased proteolytic inactivation**	**-Increased thrombogenic risk** **-No shielding from immune cells or Ab**	**-In vitro and animal model : rFIX-FX hybrid** **-Fase I : rFVIIa (BAY 86-6150)** **-Fase II : rFVIIa (NN1371)**