PEGylation: Successful Technology to Develop the Long Acting Therapeutic Biologics

제6회 파미셀 정기 학술 심포지움
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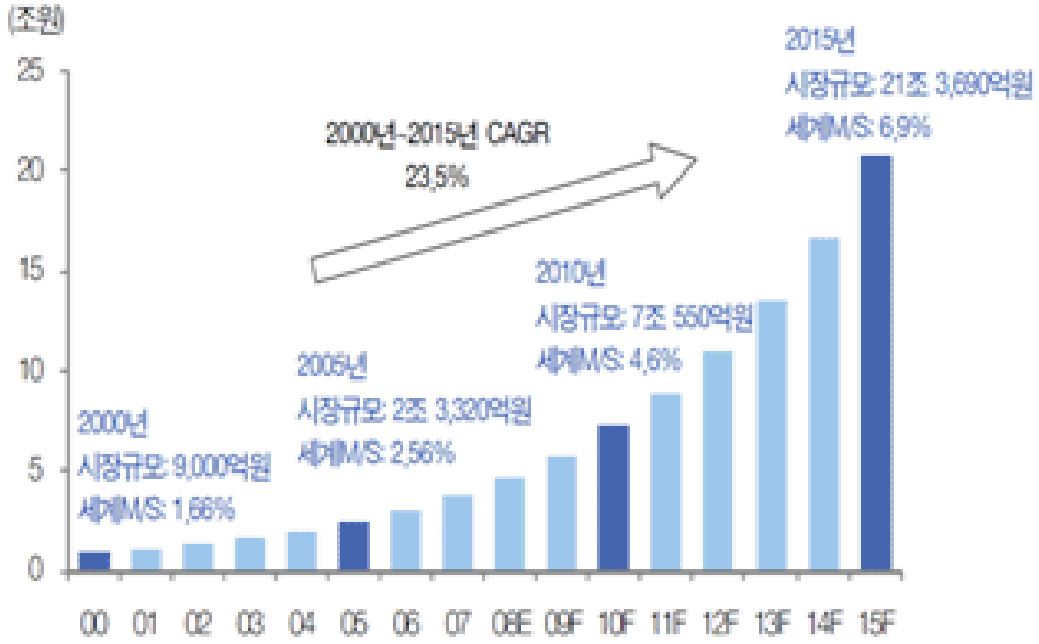
㈜바이오폴리메드(BiopolyMed Inc.,)
박 명 옥

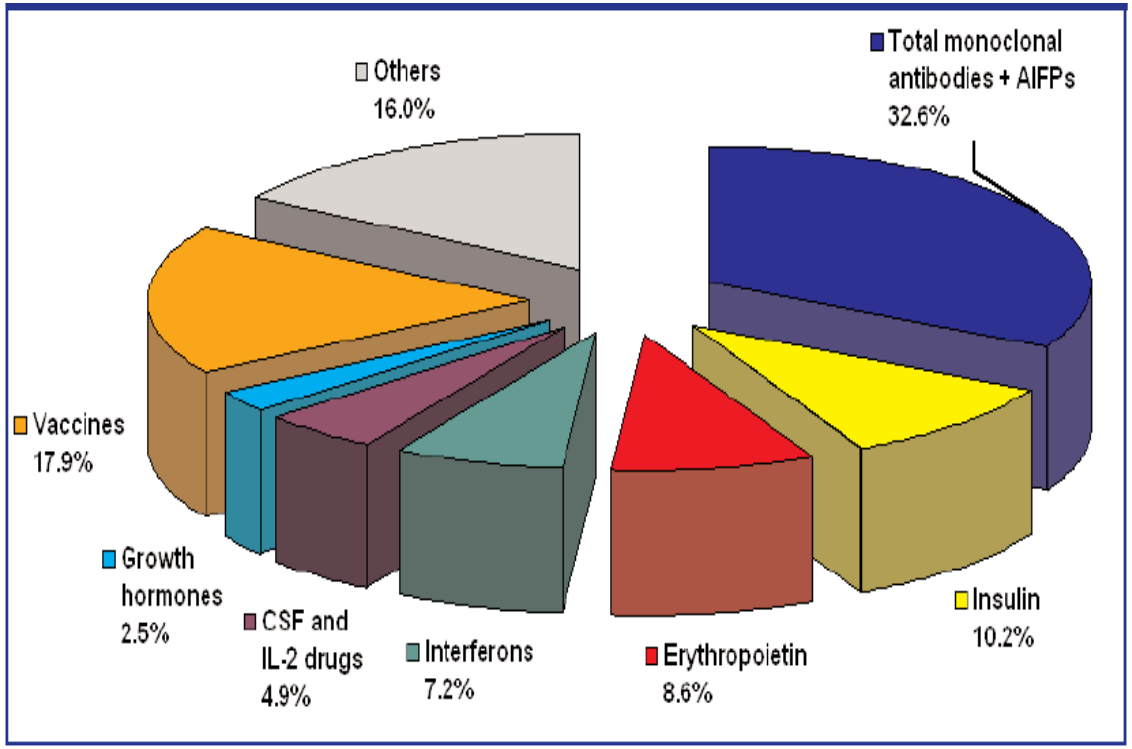
바이오신약 시장 현황과 전망

<u>시장 규모 급속 확대</u>
9천억(2000년) → 21조 4천억 (2015년) 예상

<u>국내기업 시장 점유율 확대</u>
1.66 %(2000년) → 6.9 % (2015년) 예상

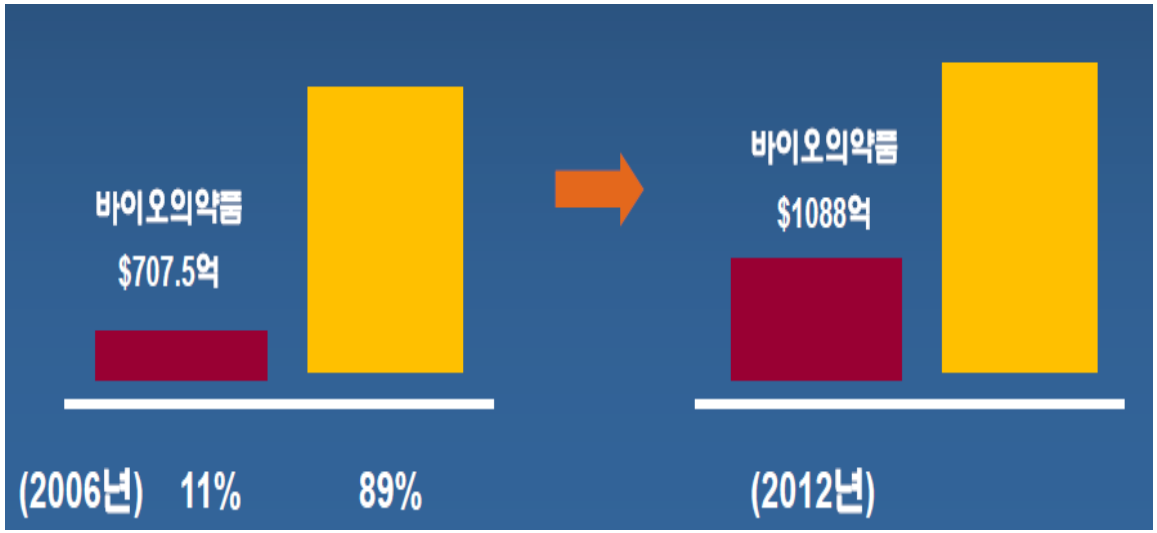


Biologic Drug Type Market Share, 2008



Source: visiongain, company annual reports and IMS Health, 2009

Market of Biotechnology



IMS Health Market Prognosis, 2010

Problems with Protein and Peptide Pharmaceuticals

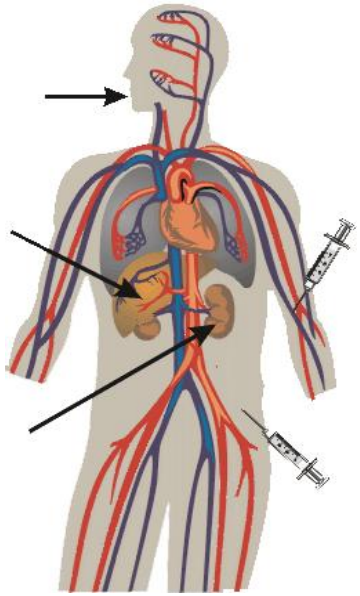
Orally inactive

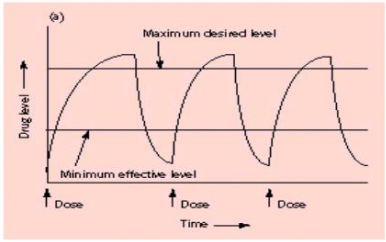
Liver uptake

Proteolytic cleavage

Kidney filtration

Insolubility

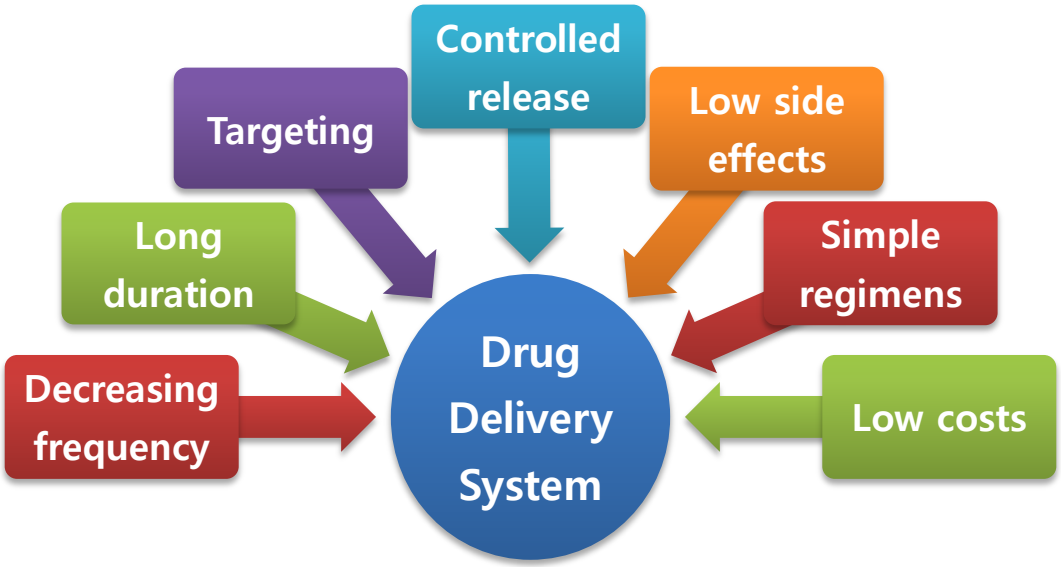




-i.v. injection: very high blood levels initially

Immunogenicity/Antigenicity

- Rapidly degraded (instability)
- Rapidly excreted in the bloodstream (short circulating half-life)
- Repeated injections (1 inj/day, 3 inj/week)-> immunological response or side effect



Physical mechanisms

- Osmosis
- Diffusion
- Erosion
- Dissolution
- Electro transport

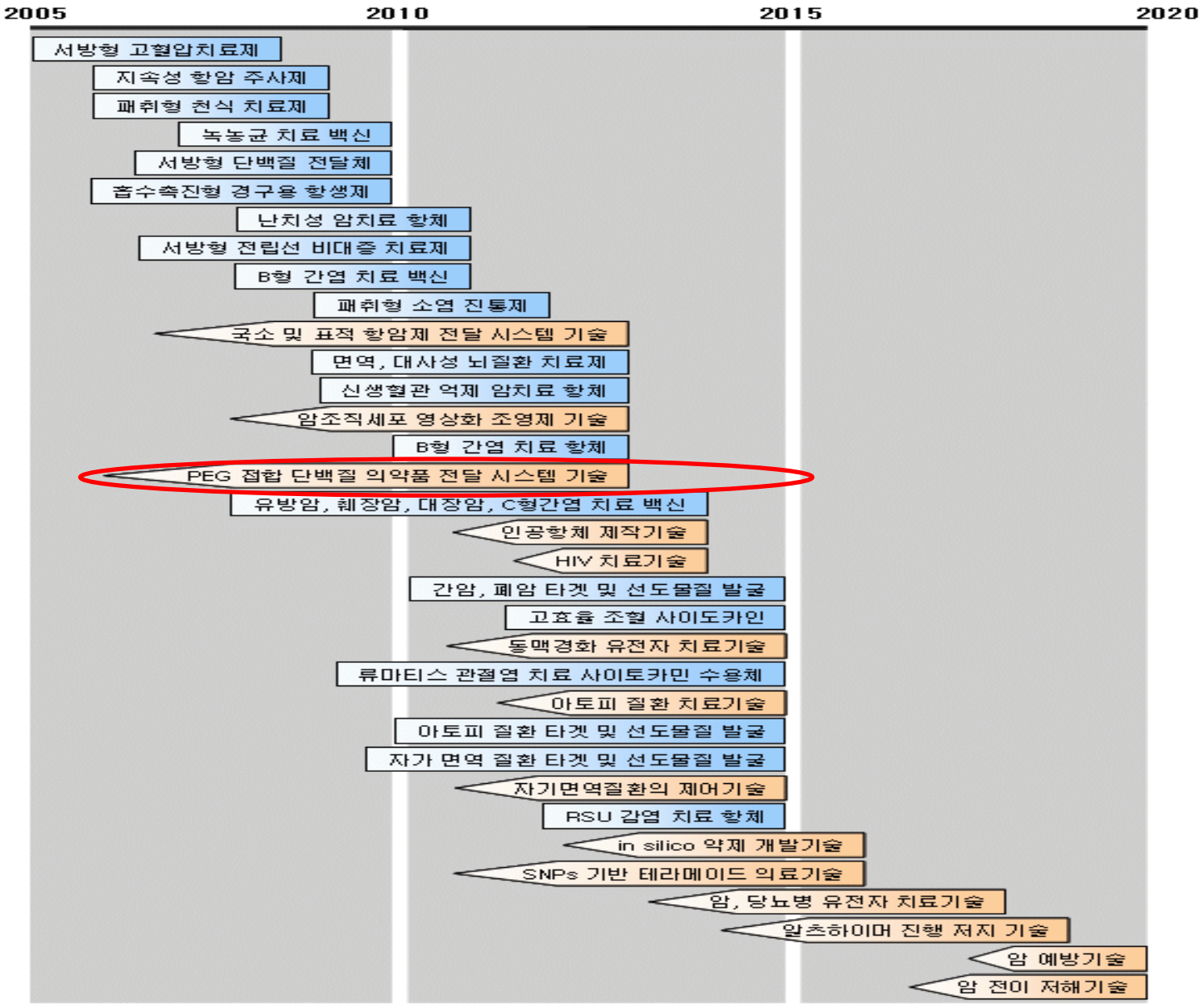
Biochemical mechanisms

- Antibody
- Gene
- Vector
- Polymer
- Particles

단백질의약품의 발전단계

바이오신약 기술 및 제품 로드맵

BiopolyMed

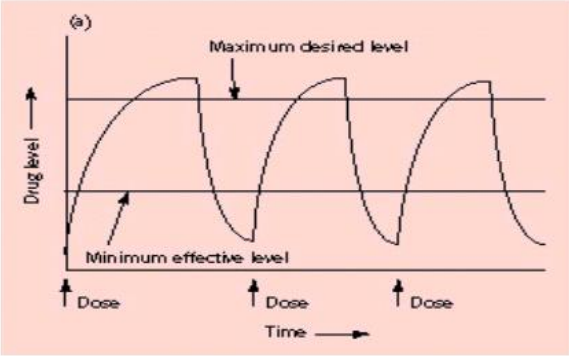


단백질의약품 개량기술 및 주요제품의 발전단계

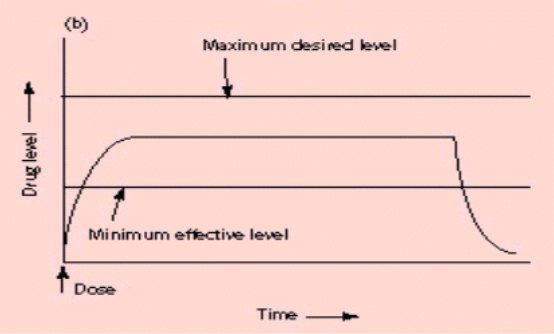
Long acting Biopharmaceuticals

"Super Biosimilar or Biobetter"

- Enhanced activity duration for short half-life drugs
- Reduction of side-effects
- Less frequent dosing-improved patient compliance
- Protecting labile drugs-improved product stability
- Potential for extended patent protection

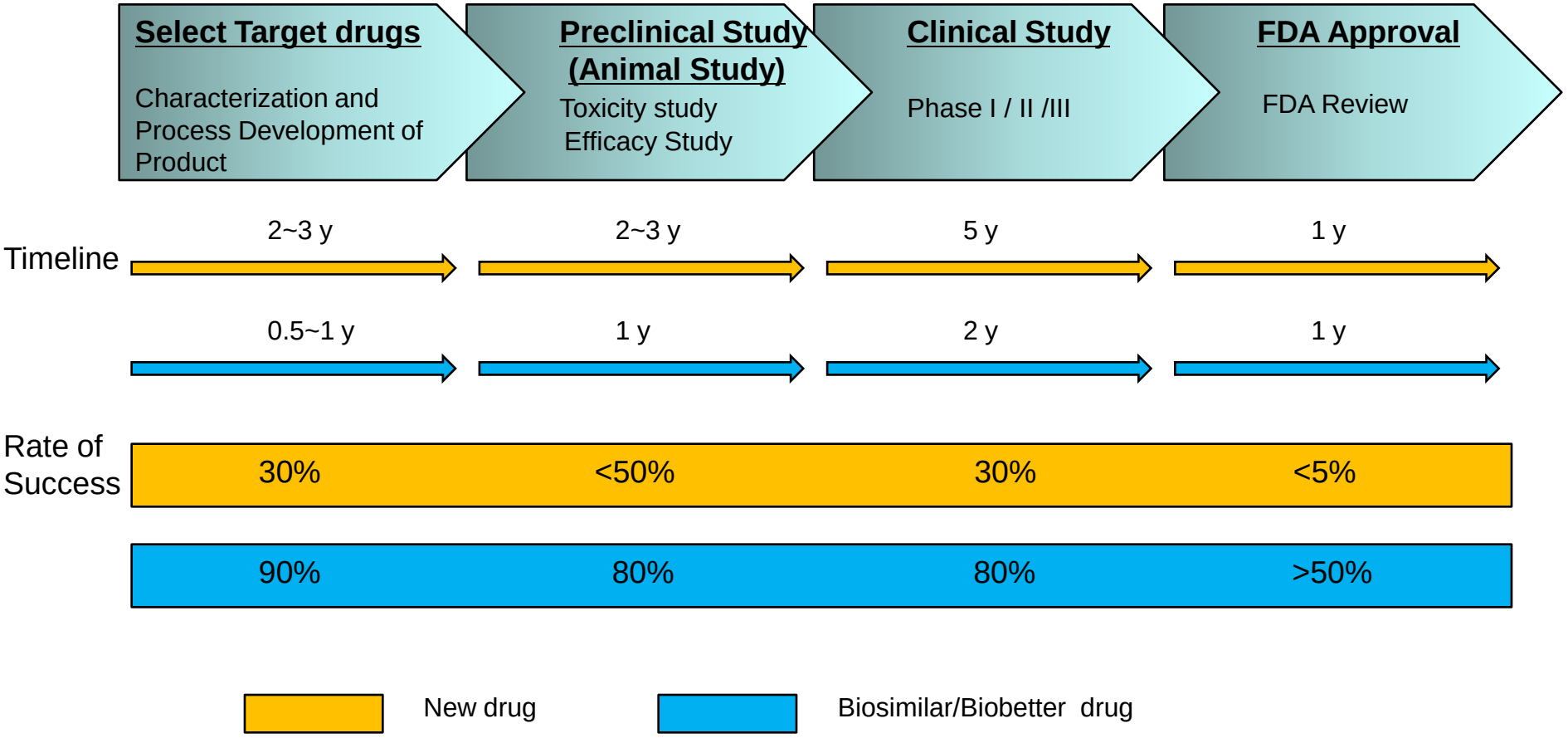


1st generation drugs



2nd generation drugs (long acting drugs)

Development of Biopharmaceutical drugs

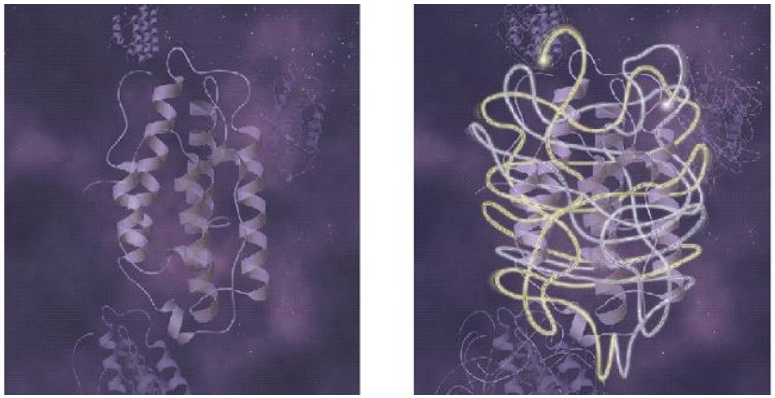


The Federation of Korean Industries(FKI), 2009

Long acting Biopharmaceuticals(launched)

Name	Brand	Patent Expiry
Epoitin	Epogen/Procrit	2012/2013
Darbepoietin	Aranesp	2014
PEG-EPO	Mircera	Launched '07
Filgrastim	Neupogen	expired
Pegfilgrastim	Neulasta	2015
Interferon alpha	Intron a Roferon a	expired
PEG-interferon alpha	PEG-Intron PEGASYS	2015

PEGylation(페길레이션) 기술



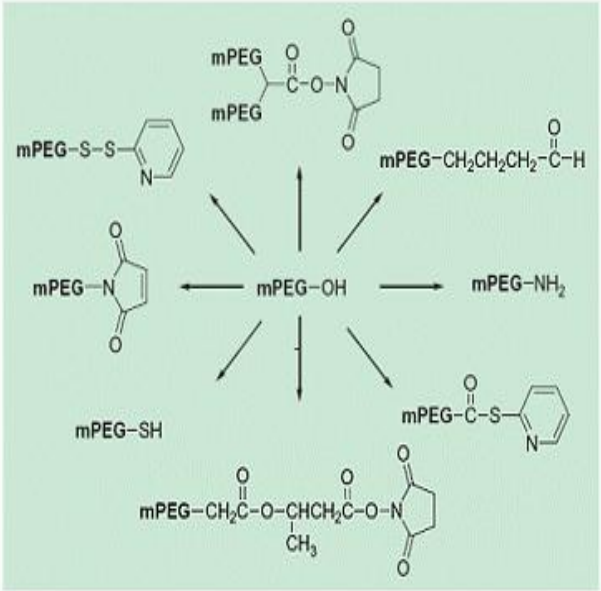
Native protein PEG-protein

•생물학적 반감기 증가→ 생체 내에서의 약효를 지속적으로 유지

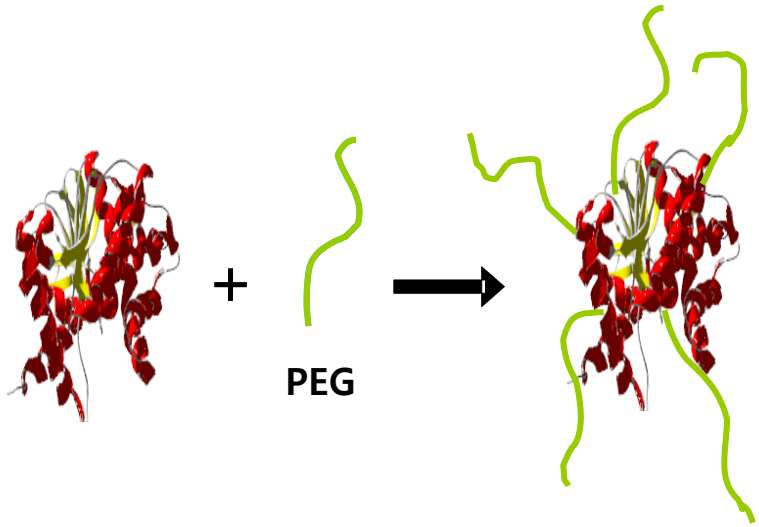
•기존의 1일1회 또는 1주3회 투여횟수에서 1주1회 또는 2주 내지 4주/1회 투여→약물의 부작용인 면역원성 및 항원성 감소

•Enzyme에 의해 쉽게 분해 → PEG shielding에 의해 안정

PEGylation Technology



Protein functional group	PEG reactive end
Amines (lysine, N-terminus)	N-hydroxysuccinimide (NHS) ester
	NHS carbonate
	aldehyde
	epoxide
	tresilate
	isocyanate
	hydrazide
	2-mercapto-thiazoline
	benzotriazole
Thiols (Cys)	maleimide
	pyridyl disulfide
	vinyl sulfone
	orthopyridyl
	iodoacetamide
Disulfides	$RO_2SCH_2C(CH_2)C(O)(C_6H_4)$



PEGs in ACTION

- **8 Approved and Marketed Products**

  - PEG-ADA (Enzon, 1990)
  - PEG-Asparaginase (Enzon, 1994)
  - Neulasta (Amgen, PEG-G-CSF)
  - PEGASYS (Nektar/Roche, peginterferon, 2002)
  - PEG-Intron (Enzon/Schering-Plough, peginterferon, 2001)
  - Somavert (Pharmacia, pegvisomant)
  - Macugen (Pfizer, VEGF antagonist,pegaptanib, age-related macular degeneration, 2004)
  - Mircera (Roche, PEG-EPO, 2007)

- PEGylated peptides and proteins of pharmaceutical interest reported

Albumin
Antibody fragments
Brain-derived neurotrophic factor
Calcitonin
EGF
Endostatin
Factor VIII
Glucagon
G-CSF

GM-CSF
GRF analogs
Hemoglobin

Hirudin
Human growth hormone (hGH)
IL-1 receptor antagonist
Insulin
Interferon-α_{2b}
Interferon-α_{2a}
Interferon-β_{1a}
Interleukin-2
Interleukin-6
KGF-2
Octeotride
PTH
Staphylokinase
tPA
Tumor Necrosis Factor (TNF)
TNF receptor type I
Uricase

단백질	물질	상품명	개발내용	적응증
Neocarsiostatin	SMANCS	Zinostatin Stimaler	Market	Hepatocellular carcinoma
Asparaginase	**PEG-L-asparaginase**	**Oncaspar**	**Market**	**Acute lymphoblastic leukemia**
G-CSF	**PEG-GCSF**	**Neulasta**	**Market**	**Prevention of neutropenia**
Adenosine Deiminase	**PEG-ADA**	**ADAGEN**	**Market**	**SCID**
IFN-alpha2a	**PEG-IFN-alpha2a**	**PEGASYS**	**Mareket**	**Hepatitis B and C**
			PEG-IFNalpha2b	Melanoma, CML and RCC
IFN-alpha2b	**PEG-IFN-alpha2b**	**PEG-Intron**	**Market**	**Hepatitis C**
			Phase I/II	Melanoma, MM and RCC
Arginine deiminase	PEG-arginine deiminase	ADI-PEG20	Phase I	Hepatocellular carcinoma
Glutaminase	PEG-glutaminase combined with DON	PEG-PGA and DON	Phase I/II	Various cancer

G-CSF: granulocyte colony stimulating factor, IFNalpha: interferon alpha, PEG: polyethylene glycol, SMANCS: styrene maleic anhydride-neocarsiostatin, ADI: arginine deiminase, DON: glutamine anti-metabolite 6-diazo-5-oxo-L-norleucine, CML: chronic myeloid leukemia, MM: multiple myeloma

Interferon-α

- Treatment of chronic Hepatitis B and C, and cancers
- Fast absorption
- Short half-life due to rapid metabolism and renal clearance
- Administered by daily or thrice weekly injections.

PEG-Interferon α

- **Developed by Schering-Plough/Enzon (2001) and Roche/Nektar (2002)**
- **Extended serum half life to 7-10 folds**
- **Reduced immunogenicity/antigenicity by PEG conjugation**
- **Administered by weekly injection**

- **Total Market: Near $2 billion/year**

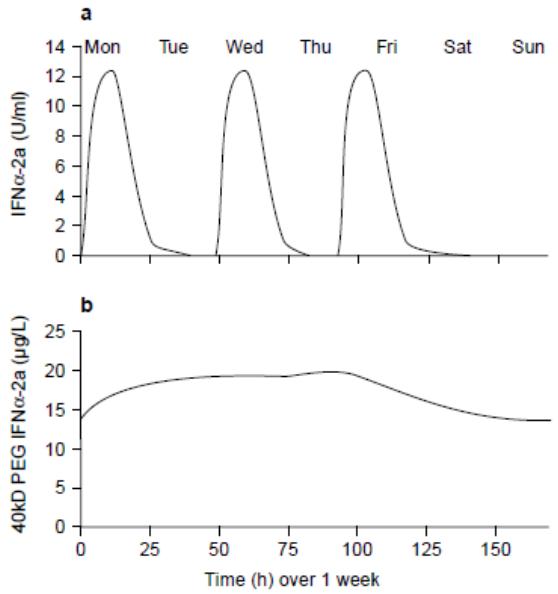
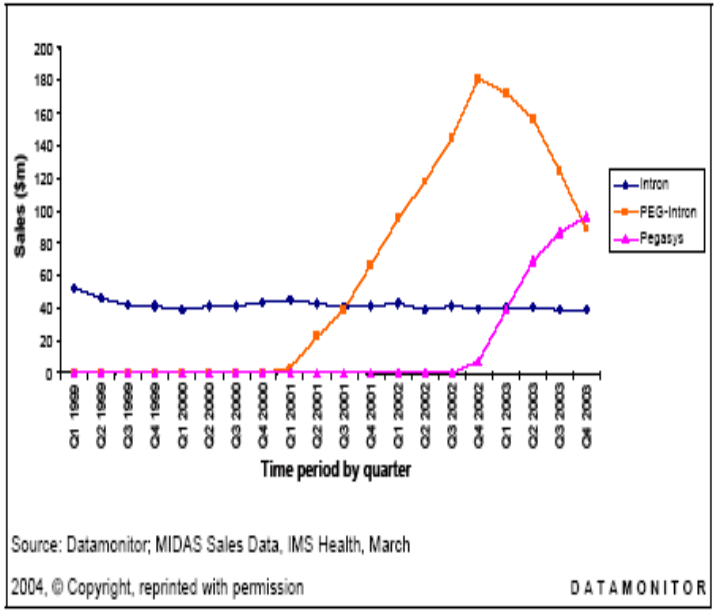


Fig. 8. Pharmacokinetic profiles for interferon (IFN)-α-2a and PEG(40kD)-IFNα-2a.

Sales of Intron, PEG-Intron and Pegasys in the US, 1999-2003:
Intron's sales have been static, while PEG-Intron's sales grew
Rapidly following its launch, but has been declining heavily since 2003



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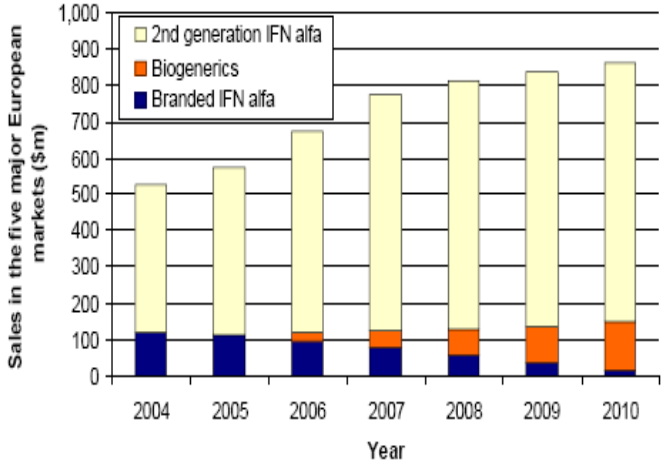
DATAMONITOR



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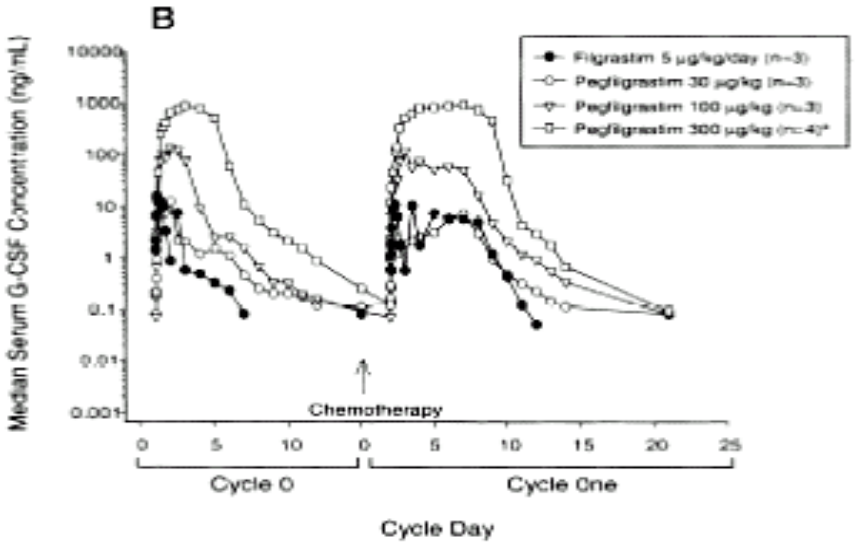
G-CSF
(Granulocyte Colony-Stimulating Factor)

- Treatment of myelosuppression associated with chemotherapy
- Required daily administration to produce a sustained increase in granulocytes during chemotherapy
  (4-8 hrs of half-life)
- Near $1.3B sale (2009)

PEG-G-CSF

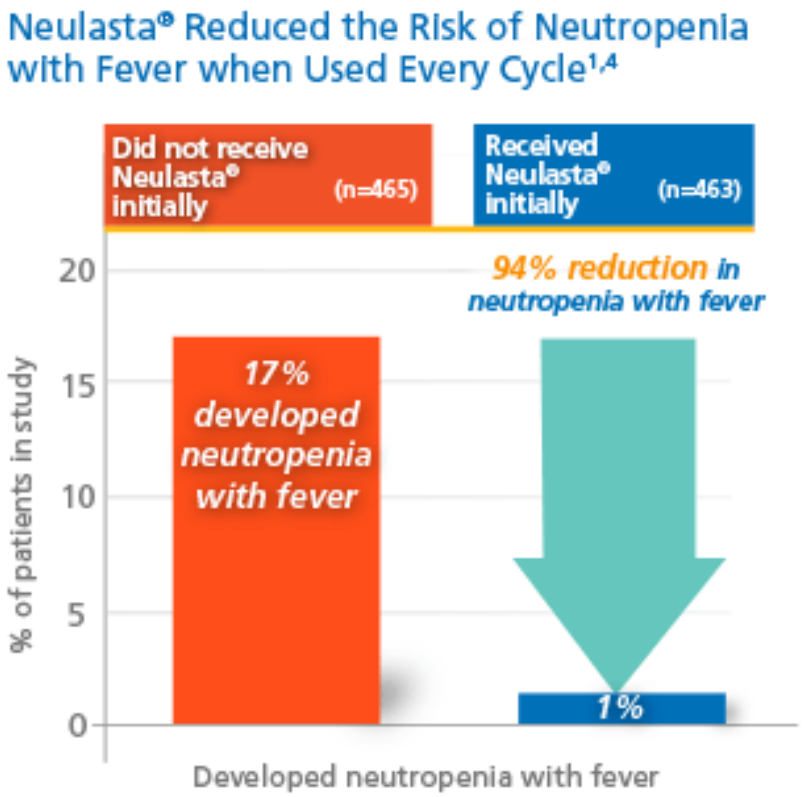
- **Covalent conjugate of rG-CSF with polyethylaene glycol**
- **Reduced renal clearance and prolonged persistence in vivo (15-80 hrs of Half-life)**
- **Required only one administration during chemotherapy**
- **Launched in 2002 (Neulasta™)**
- **$3.4 B sale (2009)**
- **Patent exp. 2015 (US &EU)**

Pharmacokinetics of PEG-G-CSF (Neulasta™)

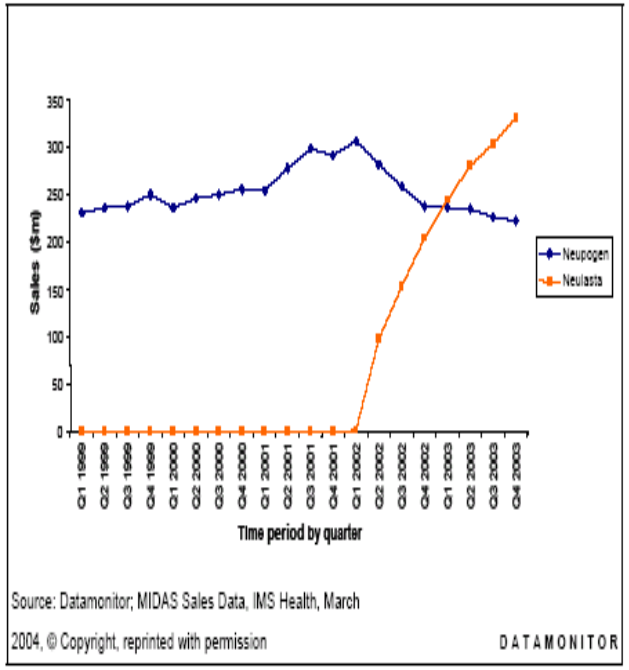


Neulasta®

- 2001에 FDA 허가
(현재 유일한 long acting G-CSF 제품)



Sales of Neupogen and Neulasta in the US, 1999-2003: Neulasta's sales were greater than Neupogen a year after its launch



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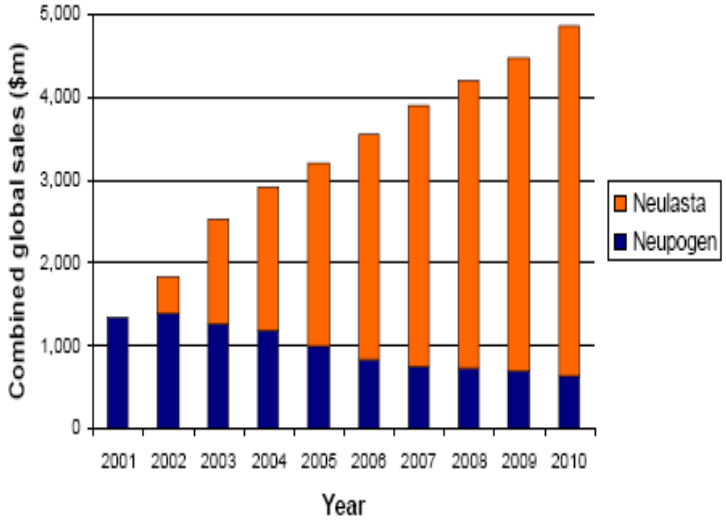


Source: Datamonitor; company-reported information

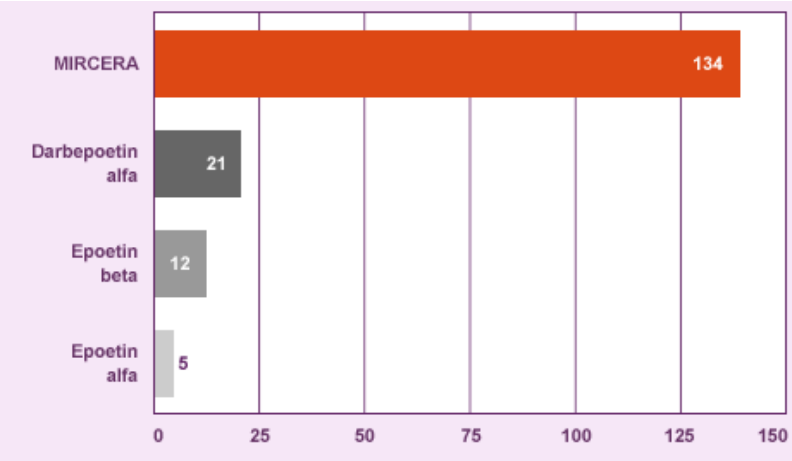
DATAMONITOR

PEG-EPO (Mircera®)

-EPO is normally produced by the kidneys
to help your body produce red blood cells
-Treatment of anemia associated with chronic kidney disease
-FDA approved in 2007 (Developed by Roche),
-sales in EU (available in 2014 in US)

-slower association to the receptor
-lower receptor binding affinity
-longer half-life (inj per 2 to 4 week)

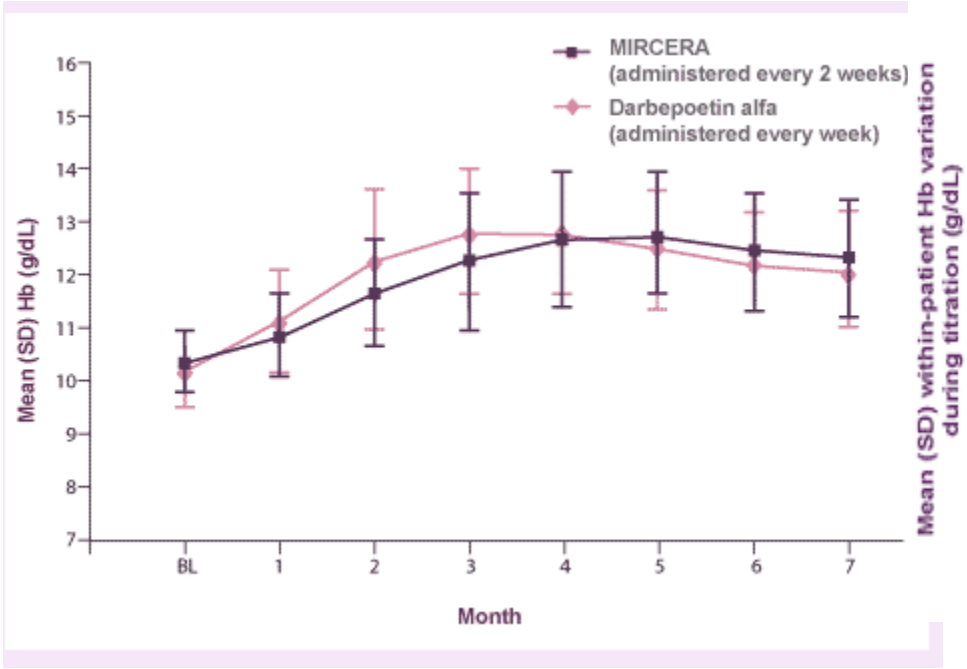
27 times longer than the half-life of epoetin alfa
6 times longer than the half-life of darbepoetin alfa

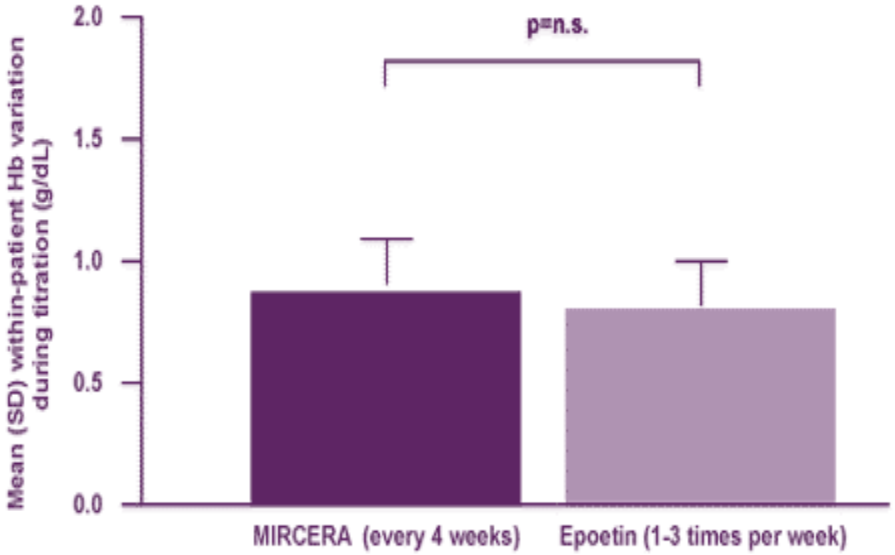


Ref) ARANESP®, was created by making 5 amino acid substitutions that add 2 additional N-linked glycosylation sites,
- once per week ($2.65B ,2009)
- Patent expired 2014 (US 2024)

www.mircera.com

PD study of PEG-EPO



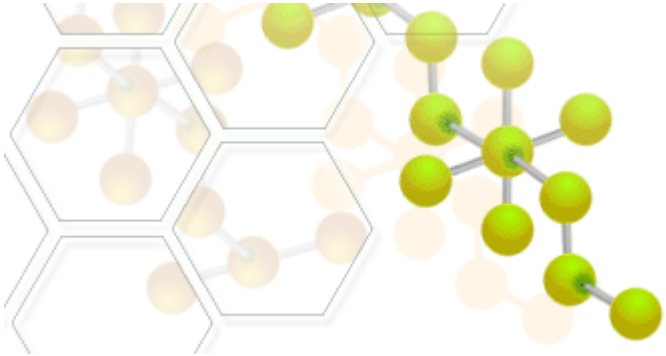


www.mircera.com

Conclusions

PEGylation:

- Extends circulating half- life and make protein drugs stay in the body longer
- Reduces toxicity and improves therapeutic efficacy
- Successful technology for the long-acting protein drugs
- Still many more protein drugs to be PEGylated to improve the drug efficacy



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