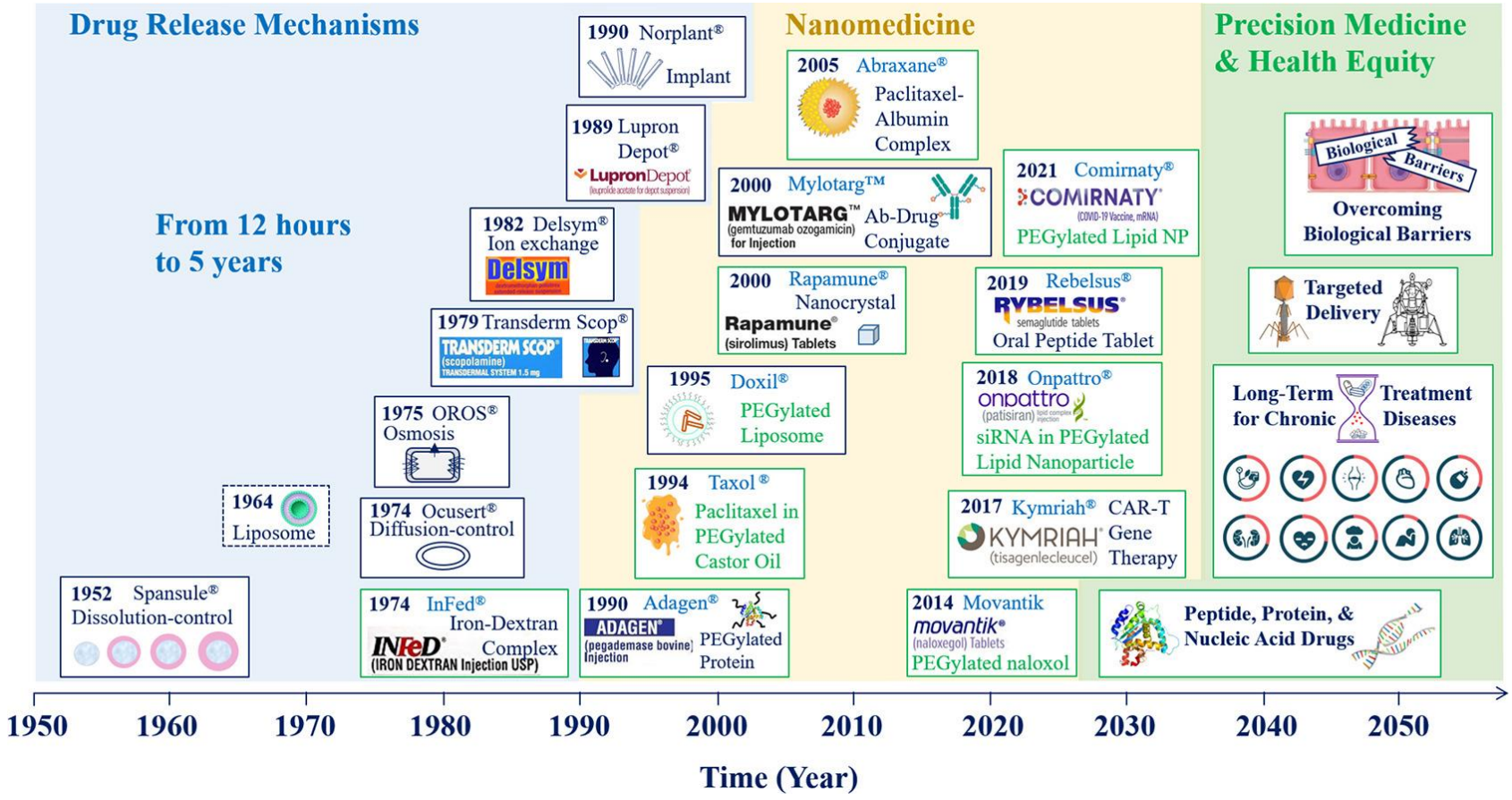
Historical Introduction to the Field of Controlled Drug Delivery

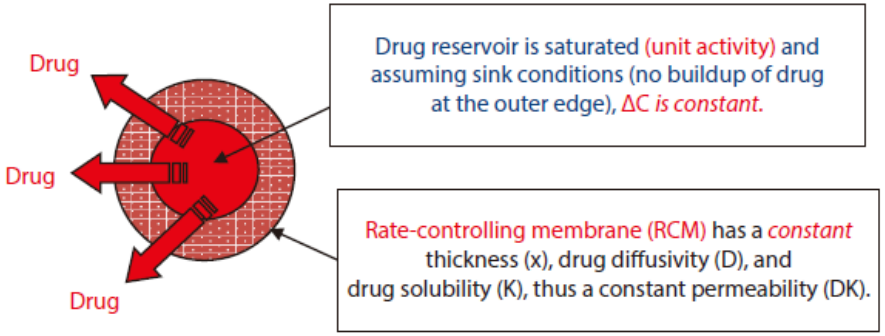


Park, K., et.al. (2022) *Journal of Controlled Release*, *342*, 157-159.

Sep. 12, 2024

Drug Diffusion through a Rate-Controlling Membrane

- Judah Folkman, an MD at Harvard University, was an early pioneer in the field of controlled drug delivery. He was circulating rabbit blood inside a Silastic® (silicone rubber [SR]) arteriovenous shunt, and when he exposed the tubing to hydrophobic anesthetic gases in the atmosphere surrounding the tubing, the rabbits went to sleep.
- He concluded that the gases were permeating across the SR tubing and absorbing into the blood.
- He proposed that sealed capsules of SR containing a drug could be implanted to act as a prolonged DDS. In this way, a *reservoir* of drug is contained within a RCM.
- The drug can diffuse out through the reservoir at a controlled rate.
- If certain conditions are filled, drug release remains constant, "zero order" with time. The principle of the RCM zero-order DDS depends on a RCM that does not vary in permeation properties over the period of use.
- Then, if the drug concentration–driving force from inside to outside of the device is constant, the delivery rate will be constant over the period of use.



$$\text{Rate of release} = \frac{k(\Delta C) \cdot D \cdot K}{x} = \text{Constant (zero order)}$$

Obituary

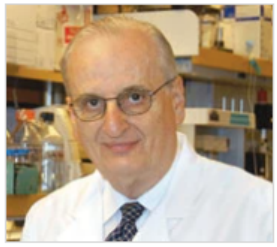
M. Judah Folkman (1933–2008)

Michael Klagsbrun & Marsha A. Moses

Nature **451**, 781(2008) | Cite this article

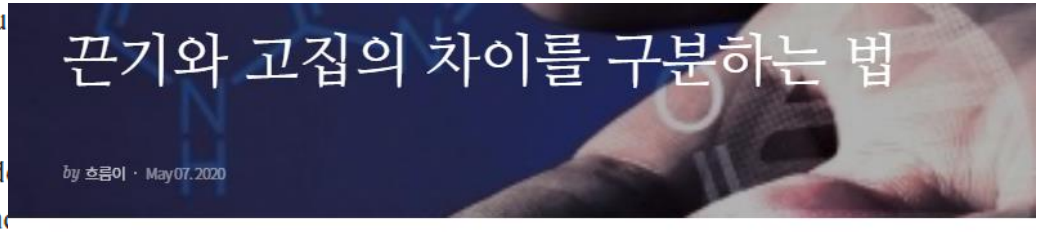
Scientist, surgeon and creator of the field of angiogenesis research.

Judah Folkman often said "Science goes where you imagine it." Few imagined more boldly or pushed science further than he did. As director of the Vascular Biology Program and a former surgeon-in-chief at the Children's Hospital Boston in Massachusetts, Folkman brought both a scientist's and a surgeon's perspectives to finding solutions to medical problems. His research observation that some tumours grow whereas others remain dormant, fused with his clinical experience in removing hot, bloody malignancies, produced a profound insight – that the recruitment of a dedicated blood su angiogenesis, is essential to tumour growth.



Credit: K. JOHNSON

Folkman's single-mindedness in demonstrating this principle red cancer biology. Furthermore, it established angiogenesis as a fun



1971년 포크먼은 암세포가 숙주와 상호작용을 한다는 아이디어를 제시했다. 암세포가 주변 조직을 속이는 신호를 내보내 종양이 자랄 수 있게 준비시킨다는 얘기였다. 이를테면 집에는 물과 가스가 들어올 파이프가 필요한 것처럼, 종양은 산소와 다른 영양분을 가져다줄 혈관이 필요하다. 포크먼은 암세포가 주변 조직에 그런 혈관을 만들라는 신호를 보낸다고 했다. 그가 내놓은 아이디어는 전혀 새로운 형태의 약, 그러니까 암세포의 신호를 차단해서 파이프를 파괴하는 약을 설계하는 것이었다. 그는 종양을 굶겨 죽일 약을 만들고자 했다.

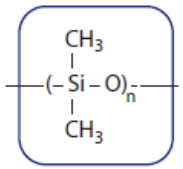
당시에는 암을 치료하는 방법으로 화학요법이 유일한 접근법이었다. 환자를 죽이지 않는 한에서, 종양에다 최대한 많은 독을 들이붓는 방식이었다. 종양과 주변 조직 사이에 있는 의문의 소통 채널을 방해하자는 아이디어는 조롱을 받았다.

https://brunch.co.kr/@nextwave7/22

Drug Diffusion through a Rate-Controlling Membrane

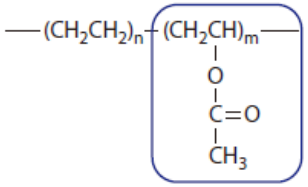
- Another key pioneer in the origin of the controlled drug delivery field was Alejandro Zaffaroni, a superb pharmaceutical chemist and entrepreneur who had collaborated with Carl Djerassi at Syntex on the synthesis of the steroid levonorgestrel, which was used in the first contraceptive pill.
- Zaffaroni had been thinking about creating a company devoted to controlled drug delivery. When he heard about Judah Folkman's work, he went to visit him in Boston and Folkman agreed to become Chairman of the company's Scientific Advisory Board. In 1968, Zaffaroni founded the very first company dedicated to the development of controlled drug delivery materials and devices, which he called Alza, after the first two letters of each of his first and last names.
- The most common materials used as RCMs in the first devices were two polymers, SR and poly(ethylene-*co*-vinyl acetate) (EVA).
- The EVA RCM is based on the copolymer of ethylene and vinyl acetate (VA). The VA disrupts the crystalline regions of the poly(ethylene) component, creating amorphous regions through which the drug can permeate (a drug cannot permeate through the crystalline region of a polymer).
- Thus, the higher the VA content of EVA, the higher the permeability of the drug through the EVA membrane. EVA RCMs may typically have as much as 40% VA.

Silicone rubber



Silicone has very high permeability to hydrophobic drugs.

Poly(ethylene-*co*-vinyl acetate) ("EVA")



The % VA controls the % crystallinity of the PE, and thereby controls the permeability of the EVA to hydrophobic drugs.

과학은 길고 인생은 짧다 [1회]

2014.12.22 18:00

0 | [강석기의 과학카페 208] 2014년 사라진 과학계 별들

<1> 알레얀드로 자파로니 (1923. 2. 27 ~ 2014. 3. 1)
붙이는 멀미약에서 DNA칩까지 개발한 생화학자

알레얀드로 자파로니. - Chemical Heritage Foundation 제공

"자파로니가 이끈다면 전 따라가겠어요."

제약업계의 미다스의 손 알레얀드로 자파로니(Alejandro Zaffaroni)는 우루과이의 수도 몬테비데오에서 태어나 대학을 마치고 미국으로 유학해 1949년 로체스터대에서 생화학으로 박사학위를 받았다. 자파로니는 미 국립보건원(NIH)에서 스테로이드화합물을 연구했다. 콜레스테롤이나 성호르몬이 바로 스테로이드다. 자파로니가 소속된 팀은 스테로이드 호르몬인 코티솔을 최초로 합성했다.

자파로니는 멕시코의 작은 제약회사 신텍스로 자리를 옮겨 스테로이드 연구를 계속했는데, 이곳에는 오스트리아 태생의 미국인 동갑내기 화학자 칼 제라시가 스테로이드 연구를 이끌고 있었다. 세계 최초로 경구피임약(활성 프로게스테론)을 만든 곳이 바로 신텍스다. 자파로니는 1962년 캘리포니아 팔로알토에 설립된 신텍스의 미국 지사 책임자가 됐다.

http://dongascience.donga.com/news.php?idx=5751

[2015년 사라진 과학계 별들](6)피임약의 아버지 '칼 제라시'

2015.12.26 09:00

★칼 제라시 (1923.10.29 ~ 2015. 1.30) 피임약의 아버지로 불렸던 화학자

칼 제라시 - Chemical Heritage Foundation 제공

1950년대 경구피임약을 최초로 개발한 화학자 칼 제라시(Carl Djerassi)는 1992년 펴낸 자서전 'The Pill, Pygmy Chimps and Degas' Horse'에서 피임약 개발의 뒷얘기를 자세히 썼다. 1995년에 '칼 제라시: 인생을 배팅하는 사람은 포커를 하지 않는다'는 제목으로 번역서가 나왔지만 현재 절판된 상태다. 이 책을 읽어보면 제라시는 꽁생원 같은 전형적인 화학자 이미지와는 180도 다른 삶은 풍운아 같은 삶을 살아온 것 같다.

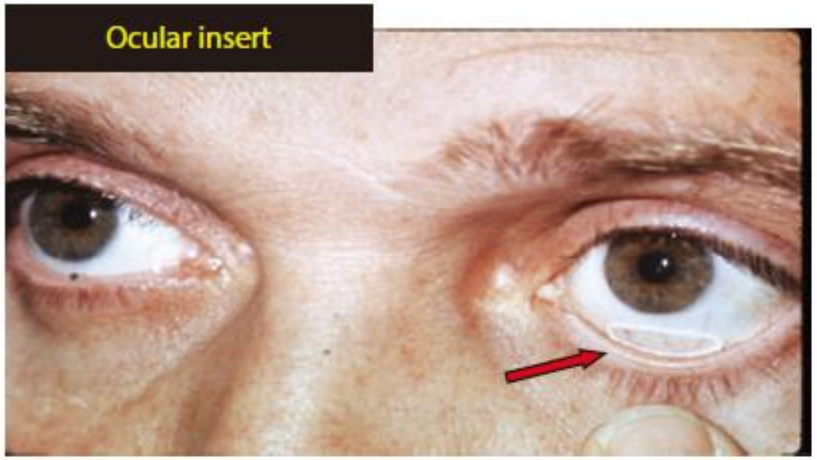
학술지 '네이처' 2014년 11월 6일자에 제라시의 새로운 자서전 'In Retrospect: From the Pill to the Pen'에 대한 서평이 실렸다. 1923년생으로 무려 91세에 쓴 네 번째 자서전이라고 한다. 한 번 읽어보고 재미있으면 아는 출판사에 번역서를 제의해볼까 잠깐 생각해봤다.

그런데 서평이 실리고 3개월이 지난 '네이처' 3월 5일자에 칼 제라시의 부고가 실렸다. 제라시가 올해 1월 30일 지병으로 타계했다는 것. 따라서 그가 죽기 3개월 전인 지난해 10월 출간된 자서전은 제라시의 마지막 작품인 셈이다.

http://dongascience.donga.com/news.php?idx=9263

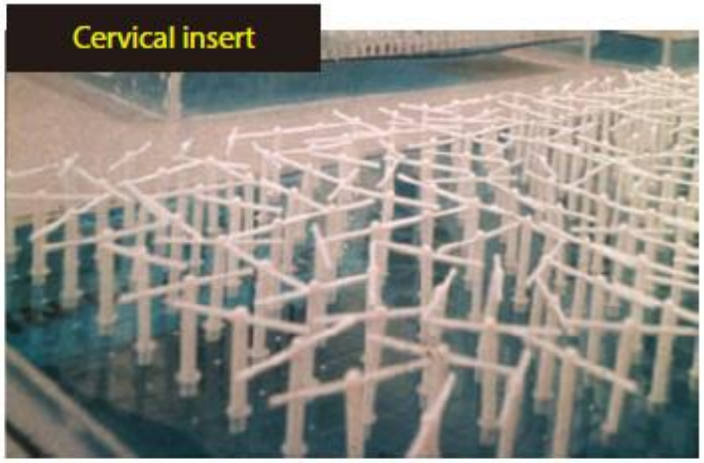
RCM DDS Products

- A number of zero-order RCM DDS were developed in the 1970s and were approved for clinical use in the 1980s–1990s.
- Typically, the drugs delivered were small and relatively hydrophobic, such as a variety of contraceptive steroids, as well as LHRH analogs (for treating prostate cancer) and pilocarpine (for treating glaucoma).
- Alza's first commercial product, the eye insert, Ocusert®, received FDA approval in 1974. The device released the antiglaucoma drug, pilocarpine, at a constant rate in the eye for 1 week, using an EVA RCM.
- An EVA RCM was also used in Alza's intrauterine device (IUD), Progestasert®, approved in 1976, which provided zero-order controlled release of the contraceptive steroid progesterone, for over a month.
- Norplant® is a controlled DDS birth control device that consisted of a set of six small (2.4 mm × 34 mm) SR capsules, each filled with 36 mg of levonorgestrel (a progestin used in many birth control pills), for s.c. implantation in the upper arm. The implanted tubes had a 5-year duration of delivery, after which they had to be explanted surgically.
- In 2006, Organon introduced a single-tube system, Implanon®, using EVA as the RCM. The implant provides controlled release of the contraceptive drug etonogestrel for up to 3 years.
- Vaginal rings were also designed as zero order, RCM, DDS. Although it did not become commercialized, this ring laid the groundwork for the subsequent development of other vaginal rings, such as the Estring® and Femring®, which were approved in the late 1990s for the delivery of estradiol acetate, in the treatment of postmenopausal urogenital symptoms. NuvaRing®, developed at Merck, is made of EVA and has been used clinically to deliver estradiol for treating postmenopausal urogenital symptoms.



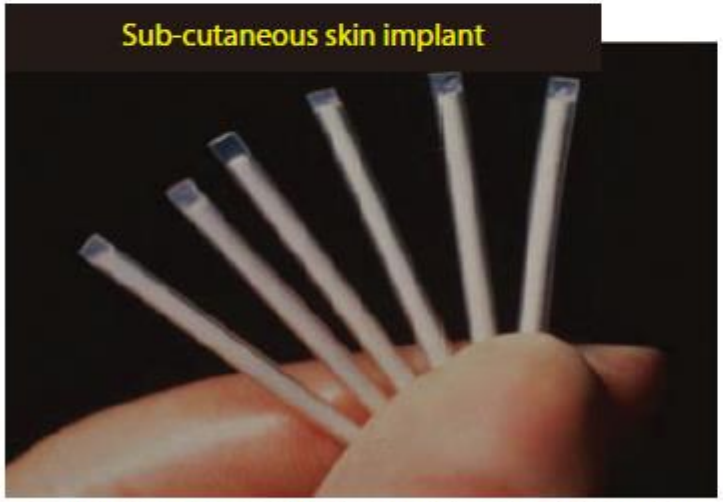
Ocusert anti-glaucoma eye insert containing pilocarpine (RCM = EVA) (Alza)

(a)



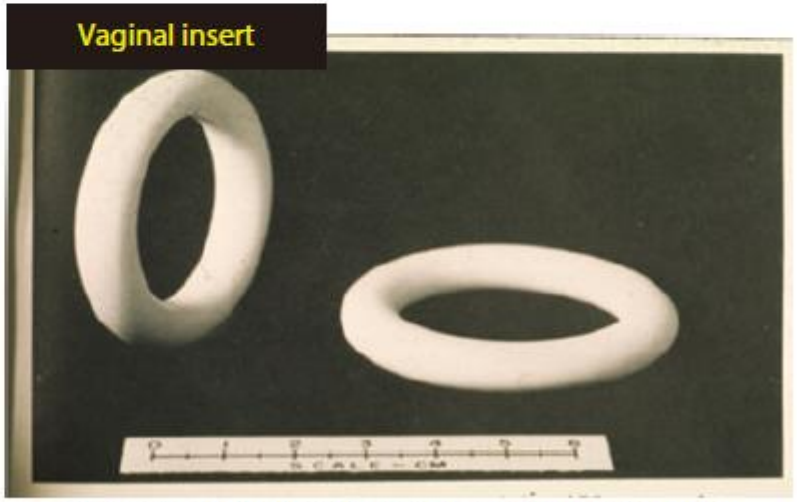
Progestesert IUD containing contraceptive steroid, progesterone (RCM = EVA) (Alza)

(b)



Norplant implant containing contraceptive steroid, levonorgestrel (RCM = SR) (Population Council, Wyeth)

(c)

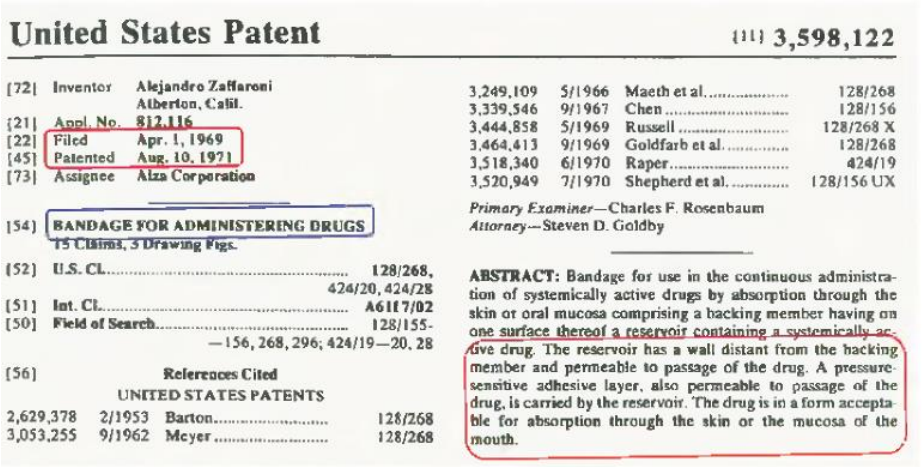


Vaginal ring insert containing contraceptive steroid, medroxy-progesterone (RCM = SR) (WHO, Upjohn)

(d)

Bandage for Administering Drugs

- The Alza skin patch is a reservoir system that incorporates two release mechanisms: an initial burst release of drug from the adhesive layer and zero-order release over an extended period (e.g., several days), facilitated by the RCM built into the patch and separating the drug reservoir from the skin surface.
- The skin patch technology is referred to as a transdermal therapeutic system (TTS).
- If the RCM does not change in properties during the contact time of the patch on the skin, the drug diffusion rate across the membrane and out of the patch will be constant. The delivery rate from the patch is designed to be much slower than the diffusion of the drug through the stratum corneum (the main resistance in the skin), thus rate control is determined by the patch and not the skin. This was referred to as "putting the major resistance to drug delivery into the device."
- The first controlled delivery skin patch commercially available was Alza's product Transderm-Scop®, approved in 1979 for the transdermal delivery of scopolamine, a drug that alleviates the discomfort of motion sickness.



United States Patent [11] 3,598,122

[72] Inventor Alejandro Zaffaroni, Atherton, Calif.
[21] Appl. No. 812,116
[22] Filed Apr. 1, 1969
[45] Patented Aug. 10, 1971
[73] Assignee Alza Corporation

[54] BANDAGE FOR ADMINISTERING DRUGS
15 Claims, 3 Drawing Figs.

[52] U.S. Cl. 128/268, 424/20, 424/28
[51] Int. Cl. A61f 7/02
[50] Field of Search 128/155-156, 268, 296; 424/19—20, 28

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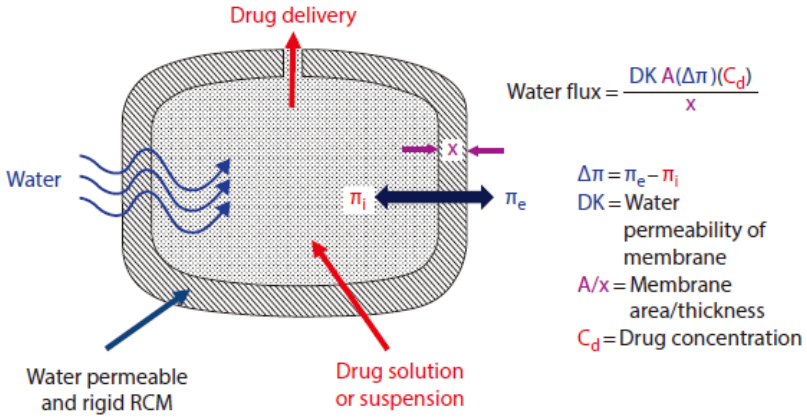
Primary Examiner—Charles F. Rosenbaum
Attorney—Steven D. Goldby

ABSTRACT: Bandage for use in the continuous administration of systemically active drugs by absorption through the skin or oral mucosa comprising a backing member having on one surface thereof a reservoir containing a systemically active drug. The reservoir has a wall distant from the backing member and permeable to passage of the drug. A pressure-sensitive adhesive layer, also permeable to passage of the drug, is carried by the reservoir. The drug is in a form acceptable for absorption through the skin or the mucosa of the mouth.

Osmotic Pressure Controlled Release

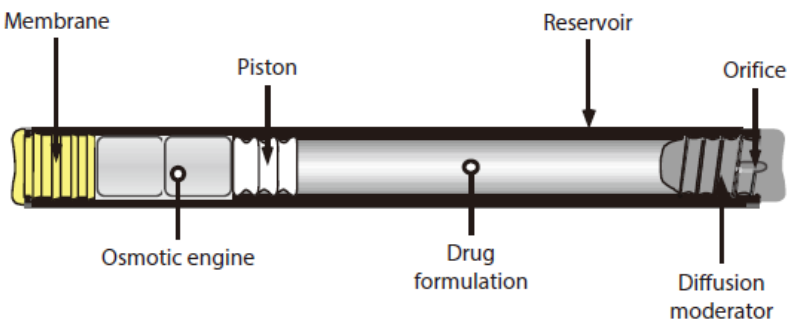
- In the 1970s, an alternative method to achieving controlled release was developed, based on the principles of the osmotic pump. It utilizes a constant volume and constant concentration (saturated) of a drug solution, or dispersion, inside a rigid, semipermeable membrane (the RCM).
- Water permeates through the RCM into the device, displacing an equal volume of drug solution out of the device, through a microscopic pore created in the membrane.
- The water permeates into the tablet due to an osmotic pressure difference between the osmotic pressure of water within the body fluids (e.g., the GI tract fluids) and the low osmotic pressure within the saturated drug condition inside. The elementary osmotic pump (EOP) was developed by Felix Theeuwes and colleagues at Alza in 1975, for controlled-release oral drug delivery.
- It is important to emphasize that, while these devices exhibit zero-order drug delivery, they operate on a completely different delivery mechanism from the diffusion-driven, RCM devices described earlier.
- For osmotic pressure control, the constant drug delivery rate is driven by a membrane controlled, constant rate of water permeation into the device (in contrast to drug diffusion out of the device, as described earlier), which displaces an equal volume of a constant concentration of drug solution through the pore and out of the device. The rate of drug diffusion across the membrane is negligible.

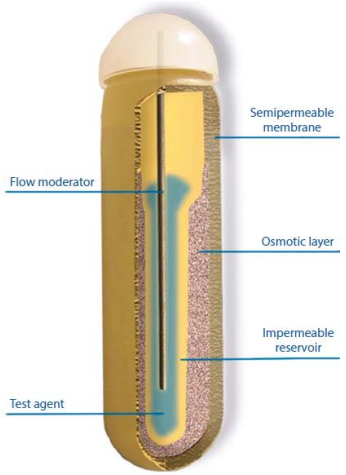


Volume of water into device = Volume of drug solution out

Osmotic Pressure Controlled Release

- The exit pore may be formed in drug tablets by a laser beam; it is built into the Duros® implant and Alzet® pump devices.
- Cellulose acetate is used for the RCM membrane of many peroral drug tablets.
- A small amount (e.g., 10%) of poly(ethylene glycol) (PEG) of ≈3 kDa MW is added to stimulate the startup of water permeation into the tablet and reduce somewhat the time lag for drug delivery from the device.
- Examples of such osmotic devices include
  1. Many types of oral tablets:
  2. The implanted Duros® titanium device,
  3. The programmable infusion pump, Alzet®, which is widely used in preclinical animal studies





LONG-ACTING INJECTABLES AND IMPLANTS

- In 1974, Robert (Bob) Langer joined the lab of Judah Folkman as a postdoctoral fellow and studied the use of nondegradable polymeric matrix systems of HEMA, EVA copolymer, and PVA, for the sustained release of proteins. In a seminal article in *Nature* in 1976, they showed the sustained release of active proteins from various EVA-based matrices in the rabbit eye -- one of the earliest depot DDS
- The nondegradable depot DDS required surgical removal and also tended to be unsuitable for the delivery of hydrophilic drugs.
- The use of degradable polymers, consisting of mixtures of drug/degradable polymer that were implanted or injected into the body and that could release drug for a sustained period of time..
- A variety of options are now possible:

  (1) long-acting injections (LAIs) of liquid dispersions of solid microparticles,

  (2) LAIs comprising solutions that subsequently form gel-like masses upon injection, due to the temperature rise or solvent dilution occurring in vivo,

  (3) s.c. implants of resorbable, polymer–drug solids, in the forms of wafers, discs, or other shapes.
- The polymers used in these systems have most often been based on poly(esters), with the most well-known, and commonly used, degradable polymers in drug delivery being polyesters based on the copolymers of lactic acid and glycolic acid, i.e., poly(lactic-co-glycolic acid) (PLGA).
- Lupron Depot® was developed by TAP Pharmaceuticals, a joint venture formed in 1977 between the Abbott Laboratories and the Japanese pharmaceutical company Takeda.
- The poly(anhydrides) are a family of hydrolytically degradable polymers used in depot DDS that were conceived and synthesized in Bob Langer's laboratory at MIT and this work led to the commercial introduction in 1995 of Gliadel®, solid wafers, or discs of poly(anhydride), loaded with the cytotoxic drug, carmustine (*bis*-chloroethylnitrosourea [BCNU]), for the treatment of brain glioblastomas.

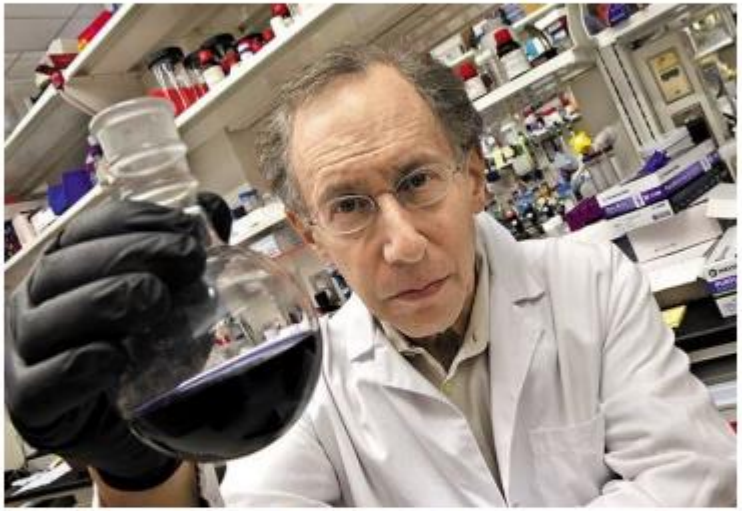
https://achievement.org/achiever/robert-s-langer-ph-d/#biography https://www.nature.com/articles/nrd1747.pdf?origin=ppub

[테크노 사이언스의 별들] 안정된 대기업 마다하고… '의학계 에디슨' 된 모더나 창업자

생명공학 분야 혁명 이끄는 로버트 랭어 미국 MIT 교수

박건형 기자

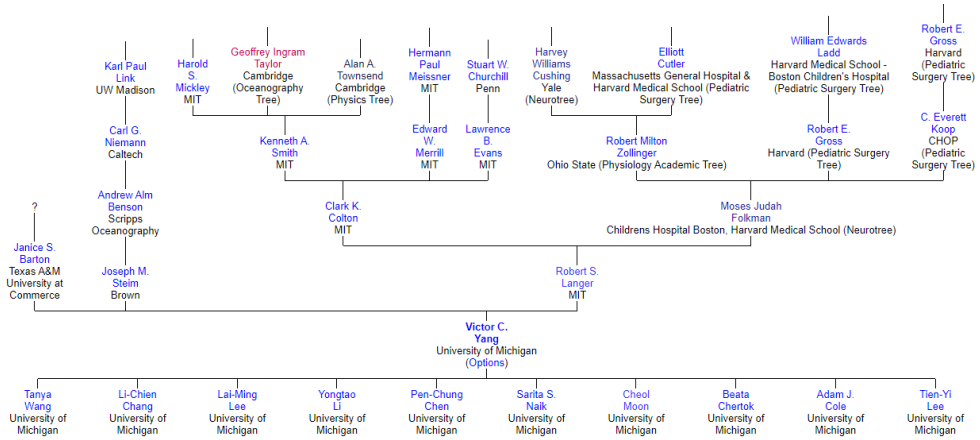
입력 2023.08.08. 03:00



미국 MIT의 랭어 랩에서 실험을 준비하고 있는 로버트 랭어 교수. 생명공학과 의학, 재료공학을 아우르는 1500건의 논문과 1400건의 특허를 갖고 있는 그는 역사상 가장 많이 인용된 엔지니어다. /게티이미지코리아

1974년은 중동전쟁이 촉발한 1차 오일쇼크가 한창이었다. 엑손·셰브론 같은 대형 석유 기업들
신제품 개발과 공정 효율화로 위기를 극복하기 위한 인재 영입에 혈안이 됐다. 하버드, 스탠퍼
유명 대학 화학공학 전공 졸업생들이 1차 타깃이었다. 그해 매사추세츠공과대(MIT)에서 박사
를 받은 코넬대 졸업생 로버트 새뮤얼 랭어 주니어(Robert Samuel Langer Jr.·1948~)도 취
제안을 20건 받았지만 모두 거절했다. "내가 배운 지식을 단순히 기업 수익률을 높이는 데 사용
고 싶지 않았다. 무엇을 할지는 몰랐지만, 사람들을 돕고 싶었다"는 이유였다.

◇석유기업 등 20곳 러브콜 모두 거절



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Lupron Depot (leuprolide acetate for depot suspension)	**TRELSTAR** (triptorelin pamoate for injectable suspension)	**Vivitrol** (naltrexone for extended-release injectable suspension)	**Signifor LAR** (pasireotide) for injectable suspension	**Lutrate Depot** (Leuprolide acetate)
1, 3, 4, 6 months, MP 1989, 1996, 1997, 2011 7.5 mg/month	1, 3, 6 months, MP 2000, 2001, 2010 3.75 mg/month	1 month MP, 2006 380 mg/month	1 month, MP, 2014 20, 40, 60 mg/month	3 months MP, 2018 22.5 mg/month
Zoladex 3-MONTH 10.8 mg DEPOT GOSERELIN ACETATE IMPLANT	**Somatulin LA** (Lanreotide acetate)	**Ozurdex** (dexamethasone intravitreal implant) 0.7 mg	**Triptodur** (triptorelin) for extended release injectable suspension	**SCENESSE** (Afamelanotide Implant)
1, 3 months SI, 1989 3.6 mg/month	2 weeks MP, 2000 30 mg/2 weeks	3 months SI, 2009 0.7 mg/3 months	6 months MP, 2017 22.5 mg/6 months	2 months SI, 2019 8 mg/month
Sandostatin LAR Depot (octreotide acetate for injectable suspension)	**Arestin** minocycline HCl 1mg MICROSPHERES	**PROPEL** MOMETASONE FUROATE IMPLANT	**Zilretta** triamcinolone acetonide extended release injectable suspension 32 mg	**DURYSTA** (bimatoprost implant) 10 mcg
1 month MP ,1998 20 mg/month	2 weeks MP ,2001 1 mg/2 weeks	1 month SI, 2011 0.37 mg/month	3 months MP, 2017 32 mg/3 months	4-6 months SI, 2020 10 μg/6 months
ATRIDOX (doxycycline hyclate) 10% Cost Effective	**Eligard** (leuprolide acetate for injectable suspension)	Once-weekly **BYDUREON BCise**	**Sublocade** (buprenorphine extended-release)	
1 week, IS ,1998 50 mg/week	1, 3, 4, 6 months IS, 2002 7.5 mg/month	1 week MP, 2012, 2017 (BCise) 2 mg/week	1 month IS, 2017 100, 300 mg/month	
Nutropin DEPOT [somatropin (rDNA origin) for injectable suspension]	**Risperdal CONSTA** risperidone Long-Acting Injection	**Lupaneta Pack** leuprolide acetate for depot suspension, 11.25 mg for intramuscular injection and norethindrone acetate tablets, 5 mg for oral administration	once-monthly **PERSERIS** (risperidone)	
1 month MP, 1999 13.5 mg/month (Discontinued)	2 weeks MP, 2003 25 mg/2 weeks	3 month MP ,2012 3.75 mg/month	1 month IS, 2018 90, 120 mg/month	

MP: Microparticle
SI: Solid implant
IS: In Situ forming implant

Injectable long-acting PLGA formulations approved by the U.S. FDA. All products are based on microparticle, in situ forming implant, and solid implant formulations.

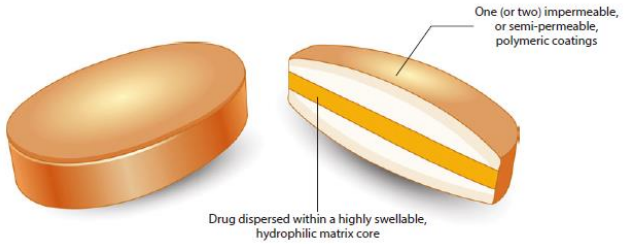
Park, H., et.al. (2022) *Journal of Controlled Release*, *342*, 53-65.

FURTHER DEVELOPMENTS IN ORAL CONTROLLED RELEASE

- The introduction of a variety of semisynthetic, and synthetic, hydrophilic, gel-forming polymers such as hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose, PEO, and Carbopol® in 1959s and 1960s.
- One of the many applications of these polymers was in the field of oral sustained release, in the preparation of "swell and gel" hydrophilic matrix DDS. In this type of DDS, a drug is dispersed in a hydrophilic polymer, such as HPMC, and compressed into a tablet.
- Sustained release of the drug is achieved as the API dissolves in the incoming fluids and then must diffuse out through the viscous, swollen, polymer chains. Nowadays, the majority of SR formulations for the oral route are based on "swell and gel" matrix tablets.
- Although easy to manufacture, drug release from this type of DDS is not zero order; instead, it typically follows first-order kinetics.
- The delivery profile of the "swell and gel" matrix tablets can be improved by modifying the geometry of the system in such a way as to effect a zero-order release rate - Geomatrix™.

$$\text{Rate of release} = \left\{ k \cdot A \left(\frac{\Delta C}{x} \right) D \cdot K \right\}$$

- "A" will increase, which will increase the delivery rate.
- ΔC/x will decrease overall, due to two processes (1) ΔC decreases because drug is being depleted from the gel and (2) the gel thickness, x, increases, as the gel swells. Both these effects will decrease ΔC/x and thus will decrease delivery rate.
- D and K of the drug should both increase with time, as water penetration and swelling increases, especially if the drug is partially polar.



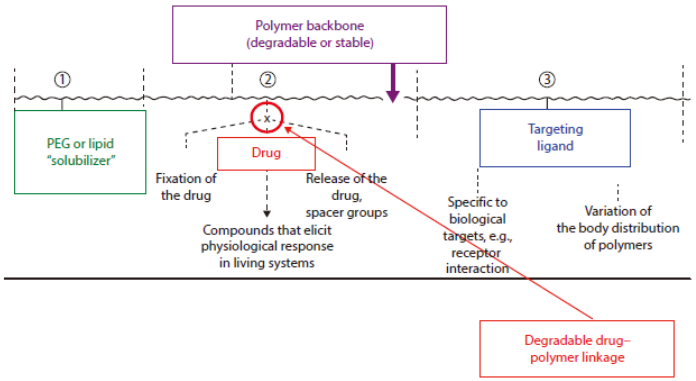
DRUGS ON SURFACES

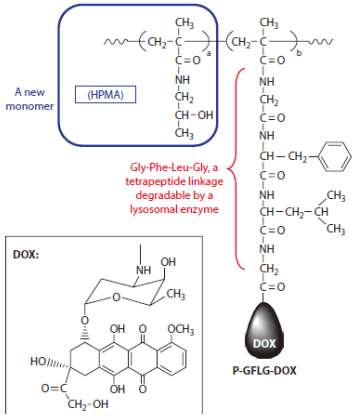
- During the 1960s–2000s, a number of different DDS were developed in which drugs were localized onto surfaces, including (1) the anticoagulant heparin, immobilized on blood-contacting surfaces; (2) drug–polymer matrices coated on drug-eluting stent (DES) surfaces; and (3) mucoadhesive-drug formulations that have enhanced residence times on mucosal surfaces.
- Heparin was the first drug directly adsorbed or linked onto a biomaterial surface. In the late 1960s, it was physically adsorbed by ionic forces to a cationic surfactant (benzalkonium chloride), which was embedded into a graphite coating on the polymer surface.
- Drug–polymer matrices have been coated onto stents and are known as drug-eluting stents, or DES. One of the earliest DES was the Cypher® stent of J&J, which was coated with a thin layer of a blend of poly(*n*-butyl methacrylate) and EVA, containing the smooth muscle cell antiproliferative drug, Sirolimus®. Taxus™, the DES of Boston Scientific and approved by FDA in 2004, uses a thermoplastic triblock elastomer poly(styrene-*b*-isobutylene*b*-styrene) (SIBS). In this device, the drug paclitaxel is dispersed primarily as discrete nanoparticles (NPs) embedded in the SIBS matrix. Paclitaxel release involves the initial dissolution of drug particles from the paclitaxel/SIBS-coating surface, which exhibits an early burst release, followed by a sustained, slower, release of paclitaxel from the bulk of the coating.
- Mucoadhesive DDS are designed to adhere to mucosal surfaces, i.e., those epithelial interfaces with an overlying mucus layer, such as the GI tract, the nose, the lungs, the eye, etc. To accomplish mucoadhesion, they are designed to interact strongly with the mucus layer, which is rich in secreted, highly hydrophilic glycoproteins. Mucoadhesive drug delivery polymers are similar to mucus in that they are highly hydrophilic, often negatively charged and highly H-bonding with the mucus layer. Poly(acrylic acid) has been a favorite mucoadhesive polymer, beginning with the seminal and pioneering work in the 1980s of Joseph Robinson and Kinam Park. Nicholas Peppas has proposed PEGylated methacrylate polymers as mucoadhesives.

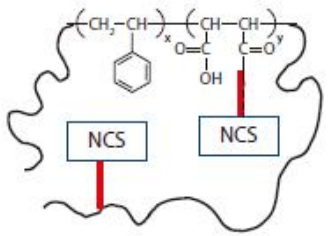
NANOSCALE DDS

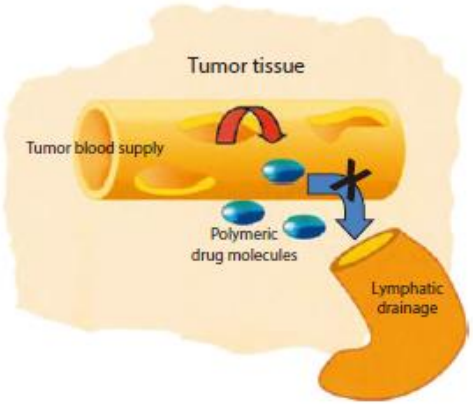
- In the 1990s, the size of controlled-release DDS scaled down again so that the *micro* systems of the previous decade made way for technologies in the *nanometer* size range.
- Three basic technologies stimulated the growth of the field of nanoscale DDS:

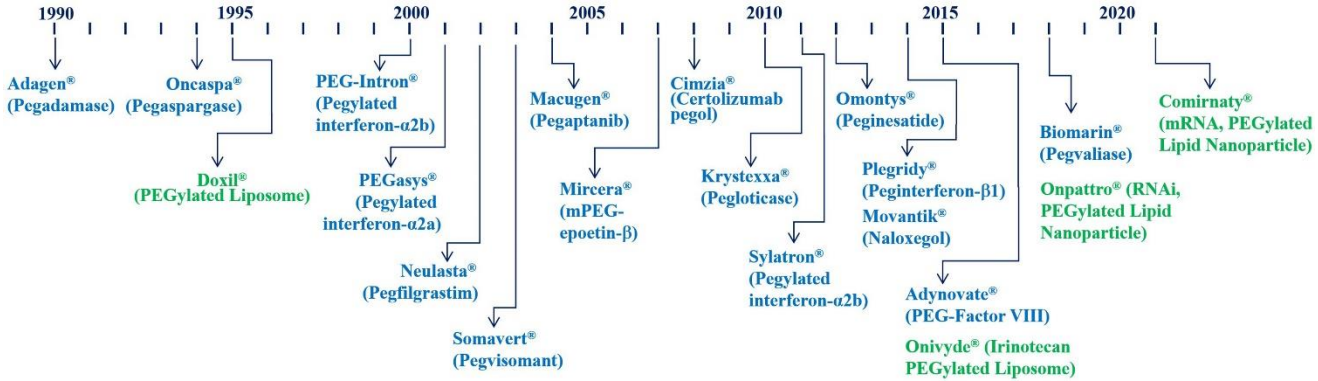
1. PEGylation, which provided protection for biomolecular drugs and extended the circulation times of the nanoDDS
2. Active targeting to specific cells, using antibodies and ligands
3. The "enhanced permeability and retention" (EPR) effect, for passive targeting to tumor tissues











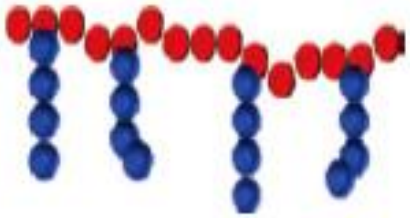
Liposomes and Nanoparticle DDS

Homopolymer (Poly A)

AB statistical (random AB copolymer)

AB diblock

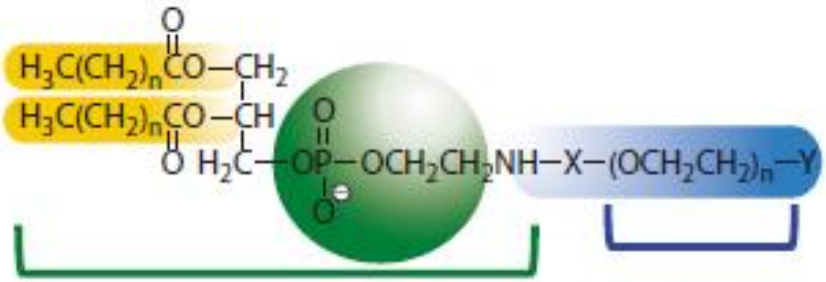
AB graft



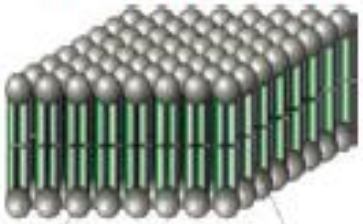
ABA triblock

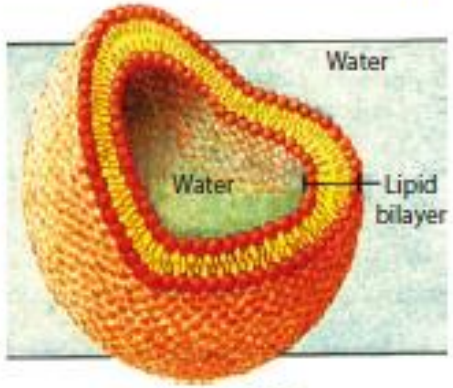
Albumin

Gold NPs



Phospholipid bilayer

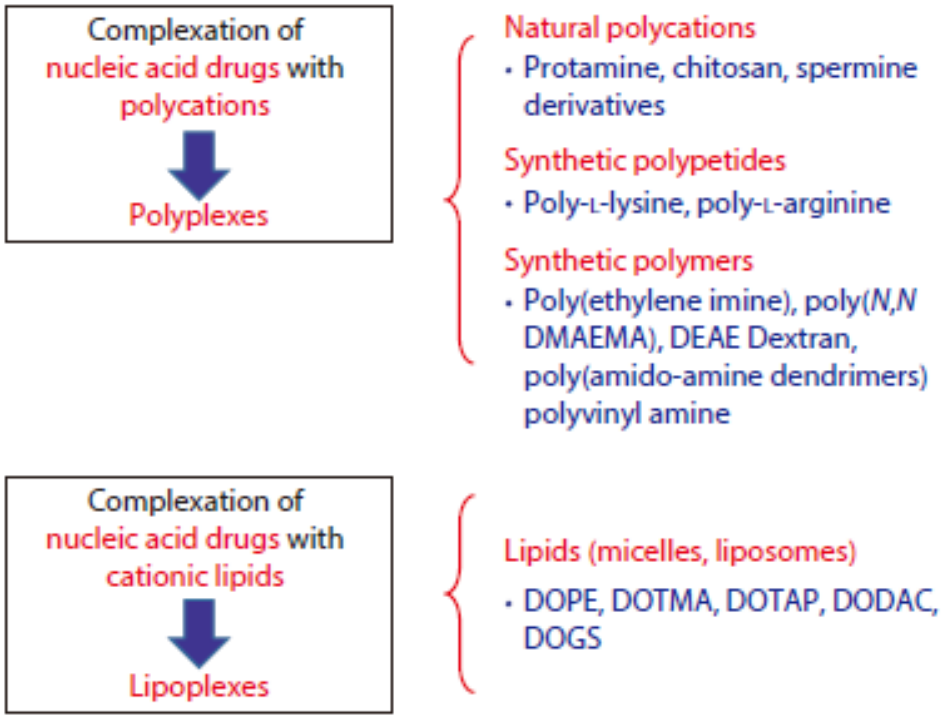




Liposome

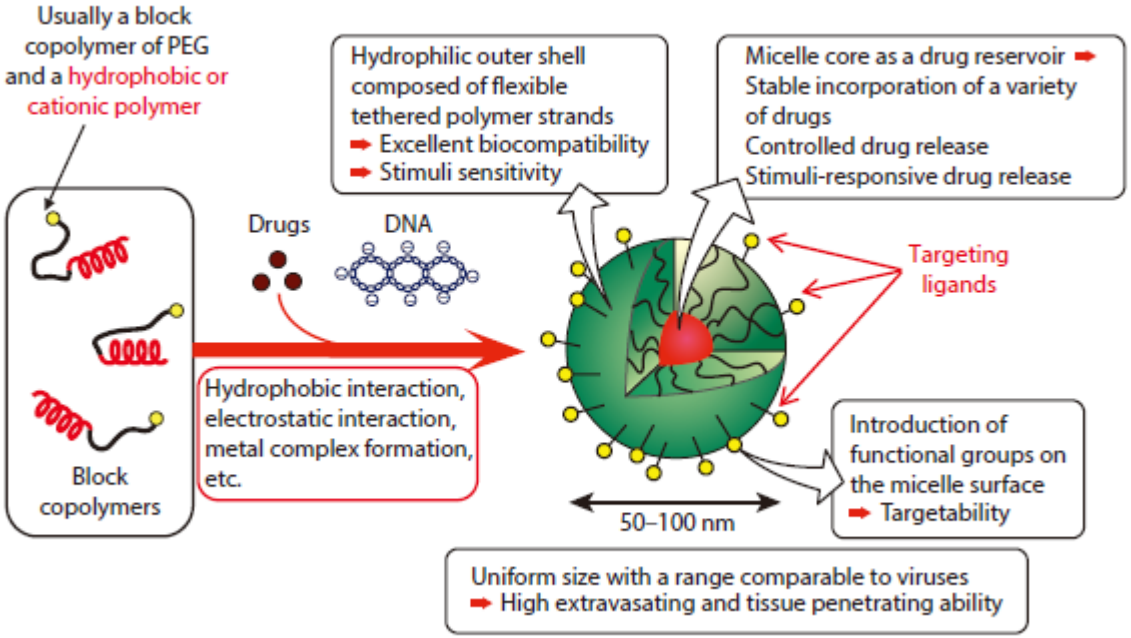
Polyplex and Lipoplex

- Cationic polymers have been used to complex negatively charged drugs, especially nucleic acid drugs, to form polyion complexes called "polyplexes."
- Important advances in the field were carried out by George and Catherine Wu who used poly(l-lysine) to complex DNA and form a polyplex, which they targeted to hepatocytes by conjugating a hepato-specific asialoglycoprotein to the carrier. Uptake of the soluble polyplex was achieved via receptormediated endocytosis, and they showed that the polyplex-delivered DNA was active within the targeted bacterial cells.
- Polycations used to form polyplexes include natural cationic polypeptides, synthetic polypeptides, and synthetic polymers. Polycations may also be cationic lipids, which form "lipoplexes" with nucleic acid drugs.



Polymeric Micelles

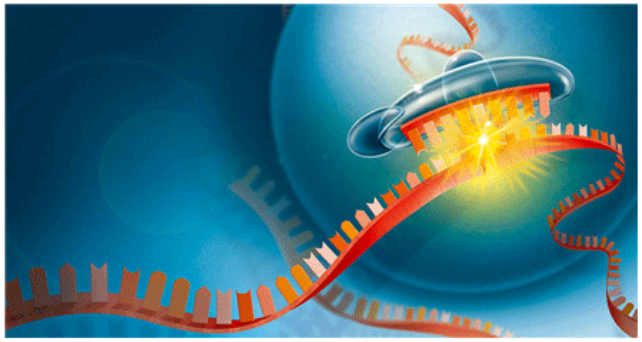
- Kataoka, Okano, and Yokoyama pioneered the development of polymeric micelle DDS. These micelles are formed by amphiphilic block copolymers, which contain both a hydrophilic polymer such as PEG and a hydrophobic polymer such as PLA or PLGA.
- These copolymers self-associate at concentrations above the critical micelle concentration to form spherical micelles in aqueous solution. The hydrophobic blocks make up the micellar core, which can accommodate a poorly soluble drug; the outer shell is composed of the flexible tethered hydrophilic polymer strands.
- The introduction of functional groups on the micelle surface allows for cell-specific targeting. An interesting block copolymer micelle is that of PEG conjugated to a cationic block that complexes with a nucleic acid drug in the core of the PEGylated micelle. A number of PEGylated polymeric micelles are in clinical trials at the present time. Several polymeric micelles have been studied with poly(HPMA), instead of PEG, as the "stealth" corona of the micelle.



[바이오토픽] 유전자를 침묵시키는 신약, 20년의 기다림 끝에 승인

의학약학 | 양병찬 (2018-08-13)

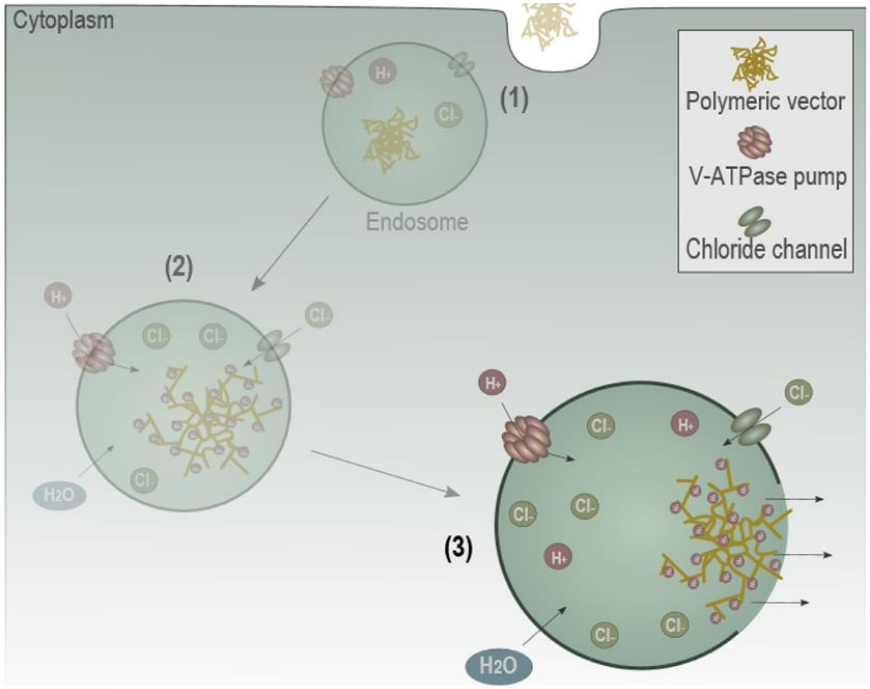
미 FDA의 결정이 RNA 간섭(RNAi) 기술에 새 생명을 불어넣을 것으로 보인다.



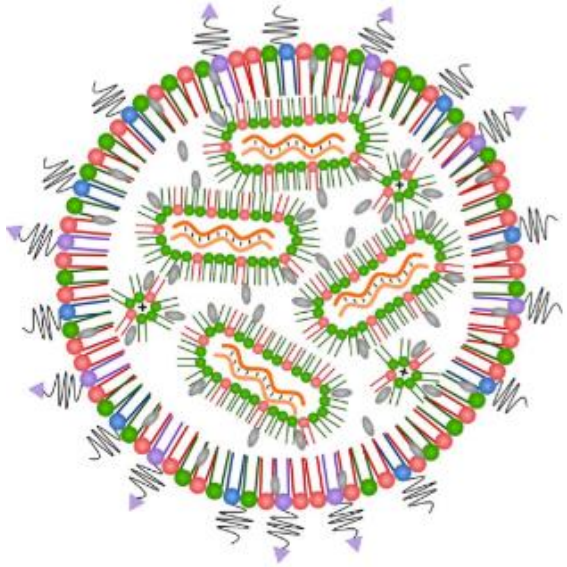
조그만 RNA 조각이 (단백질 생산에 관한 DNA의 지시사항을 전달하는) 기다란 mRNA에 달라붙어, 단백질 생성 과정을 중단시킨다. 이 천연 메커니즘을 RNA 간섭(RNAi: RNA-interference)이라고 한다. 8월 10일 새로 승인받은 약물 파티시란(patisiran)은 이 RNAi를 이용하여 특정 유전자의 스위치를 끈다. / @ ScienceNews(참고 1)

미국 식품의약국(FDA)은 「RNA 간섭(RNAi: RNA-interference) 기반 치료법」을 최초로 승인했다. RNAi란 질병과 관련된 특정 유전자를 침묵시키는 데 사용되는 기법이다. 이름하여 파티시란(patisiran)이라는 신약은 심장과 신경의 기능을 손상시키는 희귀질환을 겨냥한다.

https://www.ibric.org/myboard/read.php?id=296803&Board=news

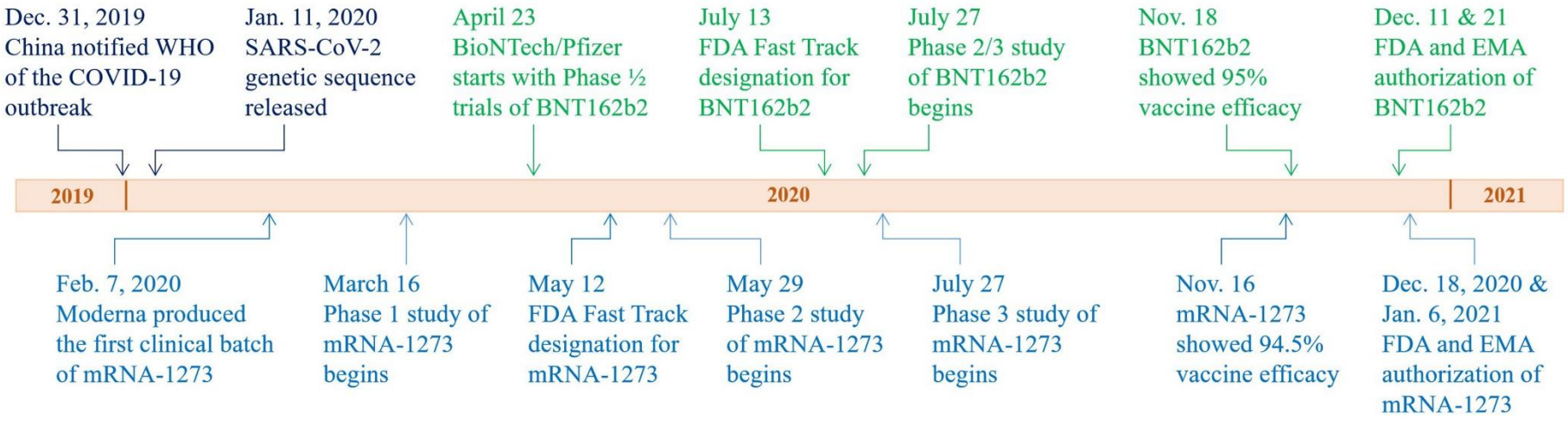


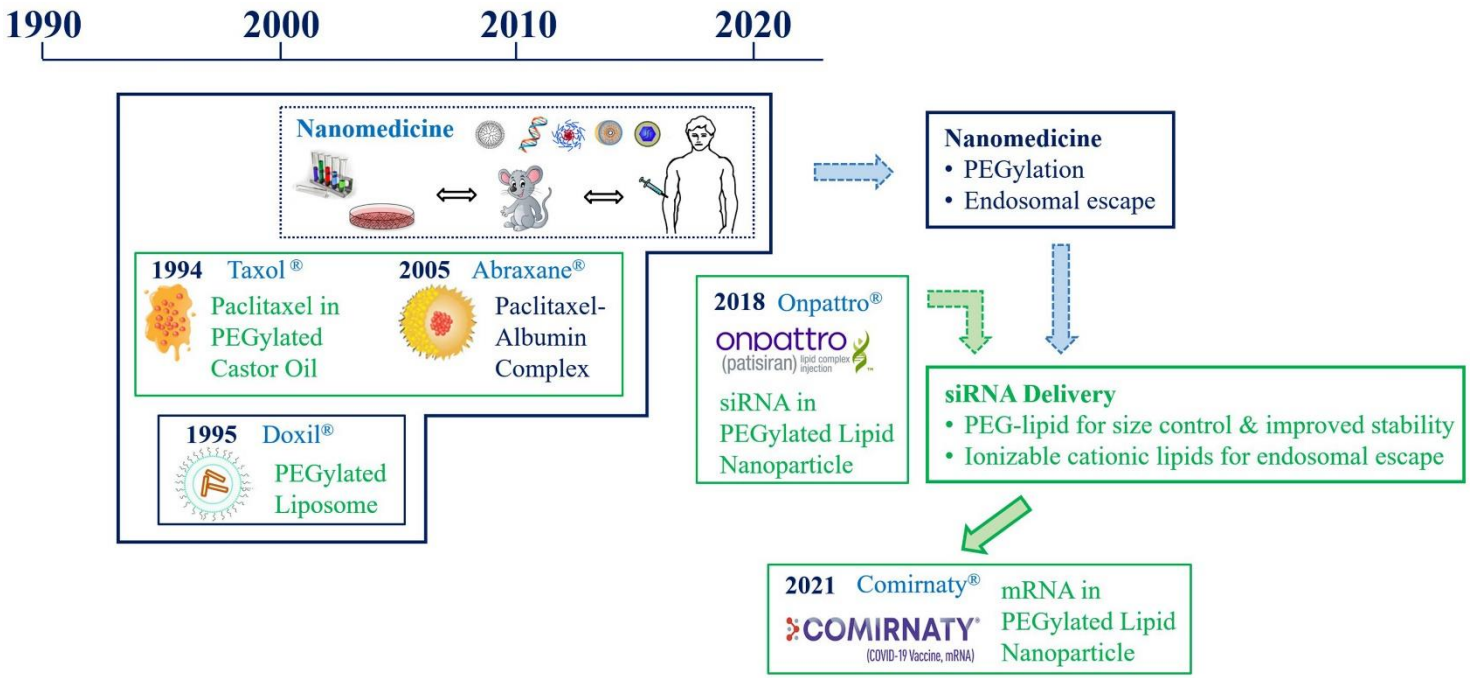
https://doi.org/10.1016/j.ejpb.2018.05.034



RNA encapsulated in lipid nanoparticles (LNPs). Cationic or ionizable lipids (shown in green) aid in encapsulating the RNA payload through electrostatic interactions. This way, the RNA is encapsulated in inverted micelles. Cholesterol (shown in grey) provides stability to the LNPs. The surface of the LNPs are generally coated with PEG (black lines). Reactive groups such as maleimide (purple triangles) can be linked to the PEG and are used to functionalize the LNPs with targeting moieties (chemical conjugation of targeting moieties)

https://doi.org/10.1016/j.tips.2020.08.004





Park, H., et.al. (2022) *Journal of Controlled Release*, *342*, 53-65.

Further Readings

- Park, H., Otte, A., & Park, K. (2022). Evolution of drug delivery systems: From 1950 to 2020 and beyond. *Journal of Controlled Release*, *342*, 53-65.
- Park, K., Otte, A., & Park, H. (2022). Perspective on drug delivery in 2050. *Journal of Controlled Release: Official Journal of the Controlled Release Society*, *344*, 157-9.