Journal of Controlled Release 285 (2018) 252–257

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

B'reshith

Ronald A. Siegel[a,*], Larry Brown[b], Elazer R. Edelman[c,d], Robert J. Linhardt[e]

[a] Departments of Pharmaceutics and Biomedical Engineering, University of Minnesota, Minneapolis, MN, United States
[b] Noveome Biotherapeutics, Inc., Pittsburgh, PA, United States
[c] Institute for Medical Engineering and Science, MIT, Cambridge, MA, United States
[d] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[e] Department of Chemistry and Chemical Biology, Department of Biology, Department of Chemical and Biological Engineering, Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, NY, United States

ARTICLE INFO

Keywords:
Early days
Langer labs

ABSTRACT

The Hebrew word "b'reshith" (בְּרֵאשִׁית) means "in the beginning". It is the first word and title of the Book of Genesis, and it describes a process of creation. The four authors were present at the beginning of Langer labs, and the purpose of this essay is to convey the scientific and technological *zeitgeist* that existed in the late 1970s and early 1980s, when Bob Langer began his exceptionally creative work. While Langer labs has branched into many other areas, Bob's unique ability to recognize important problems and entice people to look beyond their own disciplines to solve them was evident from the start. We focus on the two areas of most interest to Bob at the time, namely controlled release of macromolecules from polymers, and removal of heparin in order to prevent uncontrolled bleeding during surgery.

1. Introduction

We are a fortunate few who joined Langer Labs in the late 1970s, which for some readers was before time began. It was a small group, but it soon started its exponential growth phase. Bob Langer's group is now enormous, with hundreds of postdocs, graduate students, undergraduates, and visiting scientists. The purpose of this essay is to place Langer Labs's beginnings in the context of science and technology of the times, to recount early accomplishments, and evaluate the impact of the early work on contemporary medical research and practice.

2. How we did things

In the late 1970s there was no email and no Internet, and hence no access to instant information—we went to the library! We photocopied journal articles retrieved from library shelves, at a price per page. There was no global supply chain, and no just-in-time delivery. Phones, which were used only for talking, and phone services were purchased from a monopoly. Long distance calls were expensive. Personal computers were new, but they lacked windows capabilities, and software for what are now essential applications (they were not called "apps") such as word processing and artwork was rudimentary. "Data processing" was carried out on large mainframe computers or smaller (but still large by present standards) "minicomputers," and people usually wrote their own programs. Tapes and disks could store megabytes of data, in contrast to the gigabytes that can be carried in one's pocket on today's flash drives. Access to computers was by punch cards or by terminals, and data rates were slow. Today's laptops are as fast as the giant "supercomputers" of the 1970s.

How did we write papers and grant proposals? We typed manuscripts ourselves or hired a typist, using erasers or whiteout for corrections. Successive drafts were retyped or physically cut and pasted. (Here we particularly relied on skilled secretaries.) Simple graphs were prepared with graph paper, pens, rulers, stencils, and palettes of stick-on symbols. More complicated graphs could be prepared under computer control using a dedicated plotter, which operated using rollers and a pen carriage. Illustrations were usually drawn by medical artists on onion-skin paper and then photographed. Once the text and figures were combined into the finalized manuscript, several photocopies were assembled and mailed, in a thick envelope, to the journal editor, who then sent individual copies to the reviewers. Similarly, podium talks required preparation of photographic slides well in advance. Posters were prepared frame by frame, as the present day large roll photographic printing methods were not available. Grants were often hand-delivered to the NIH after a flight to Bethesda to meet deadlines.

Interfacing of computers to laboratory equipment was also rudimentary. Large and cumbersome cables connected instruments to the computer. Data provided from instruments was often copied into a

* Corresponding author.
E-mail address: siege017@umn.edu (R.A. Siegel).

https://doi.org/10.1016/j.jconrel.2018.07.005
Received 1 May 2018; Received in revised form 30 May 2018; Accepted 2 July 2018
Available online 03 July 2018
0168-3659/ © 2018 Elsevier B.V. All rights reserved.

notebook from an analog gauge or a digital readout. There were few software systems for facile uploading, processing and display of data, and the automatic plotters alluded to above had to be programmed by the user. Liquid chromatography took hours and individual samples were collected into test tubes placed in a rotary fraction collector. Each test tube had to be read on a UV/Vis spectrophotometer. Spectra and chromatograms were recorded on paper, and peak areas were "calculated" by carefully cutting them out and weighing them! Controlled release studies relied on UV/Vis spectroscopy and mass balances to measure mass loss.

The first HPLC instruments were making their appearance, while mass spectrometry and nuclear magnetic resonance spectroscopy were not yet applicable for the analysis of biomolecules such as proteins. Hyphenated techniques, such as LC-MS, TOF-SIMS, and MALDI-TOF were just being developed by analytical chemists, but their impact had not yet been felt in biology. Flow cytometry was just coming on line. Autosamplers and fraction collectors had to be carefully monitored, as they often failed. Molecular biology and recombinant technology were new and only recently applied in biomedical research. Fermenters lacked computer control, and we built our own dissolved oxygen probes. Confocal microscopy, micro-CT and MRI were not yet available, and three-dimensional reconstructions of materials were carried out by serial microtoming, with care taken to line up sections using "fiducial points." Molecular modeling was rudimentary, and molecular graphics capabilities were yet to be developed. In short, many techniques that we take for granted now were either non-existent or not ready for prime time.

Research was considerably more labor intensive and scientists and engineers were less productive than they are today. Despite these limitations (which did not seem like limitations then), the Langer lab of the late 1970s early 1980s made advances with remarkable speed owing to its focus on important problems and the combined use of practical solutions with a strong reliance on basic science.

3. Drug delivery and biotechnology

Many consider the modern era of polymer based drug delivery to have begun with the publication of the Higuchi equation describing the release of solid drug from solid matrices [1]. The quantitative approach taken by Takeru and William I. Higuchi and others in the 1960s and early 1970s, coupled with the development of analytical techniques such as HPLC, and the emergence of pharmacokinetics as a discipline [2], allowed drug developers to make precise and testable predictions relating drug release to the time course of drug concentrations in the body. The Alza Corporation, founded in the late 1960s, developed drug delivery technologies that could release small molecules at precise and constant rates, providing controllable blood levels within the desired therapeutic window. Osmotic pumps, along with reservoir/membrane and monolithic diffusion controlled systems (including transdermals) were developed by that company, while others endeavored to piggyback drug delivery functions onto devices such as contact lenses and biodegradable sutures.

Why only small molecules? In 1977, the biotechnology field was in its infancy. That same year, somatostatin became the first recombinant human protein synthesized by recombinant DNA technology [3], soon followed by insulin [4]. Until then, proteins had to be extracted from natural sources and purified, often a herculean effort, with yields too small to be used in therapies. This situation changed drastically *circa* 1970–1975 with the discovery of restriction enzymes and the development of monoclonal antibodies. Shortly thereafter, the biotechnology industry was born, with companies such as Genentech, Amgen, and Biogen leading the way. Delivery was a problem, however. Proteins could not be taken orally, due to hydrolysis in the gastrointestinal tract. Because of their short half-lives, injection was not feasible. Fortunately, many proteins were extremely potent, meaning that circulating levels could be low, if only they could be sustained.

During this period, Bob Langer was searching for anti-angiogenic factors, working with the renowned surgeon, Dr. Judah Folkman. Bob developed an assay with extracts of cartilage, an avascular tissue, incorporated into pellets made from ELVAX-40, a paint resin produced by Dupont. With proper cleaning, this polymer (ethylene-vinyl acetate copolymer, EVAc) was not inflammatory. Placing a pouch of tumor cells in rabbit cornea, blood vessels were seen to grow toward the tumor from the limbus. Interposing an extract-loaded EVAc pellet between a pouch and the conjunctiva, it was possible to determine whether the implant was releasing an anti-angiogenic factor. When inhibition of vessel growth was observed, the extract could be further purified and tested again in another pellet, with multiple iterations. Since it was believed, and later confirmed, that anti-angiogenic factors were proteins, this assay demonstrated the feasibility of using polymers to control the release of proteins. In a landmark paper published in *Nature*, Langer and Folkman demonstrated release, over many months, of a diverse set of proteins, along with DNA, from EVAc pellets [5]. Among other things, this was significant insofar as it suggested a means of delivering the newly abundant products of the biotechnology industry. This was the nexus at which the present authors became involved in Bob Langer's research.

4. What was the release mechanism?

At the time of the Langer/Folkman paper, it was received wisdom that proteins (indeed any molecule with MW > 500) were simply too large to diffuse through hydrophobic polymers such as EVAc. However, the procedure for forming the pellets (which we shall call matrices) involved suspension of protein powder in EVAc dissolved in an organic solvent, methylene chloride, followed by solvent evaporation. The result was a random, solid dispersion of powder granules embedded in a continuous polymer phase. This morphology was confirmed by photomicrographs taken by Rajan S. Bawa, who demonstrated the two-phase nature of the matrices before protein release [6]. After release, Bawa's

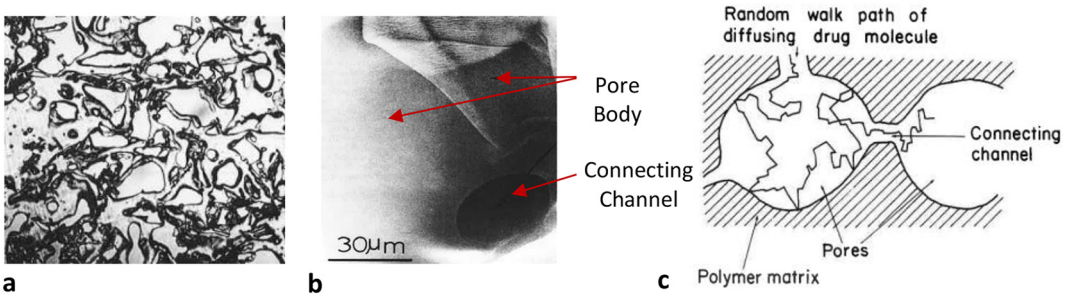

Fig. 1. a) Light micrograph taken from a thin (5 μm) section of an EVAc matrix following protein drug release, illustrating a porous carcass. b) SEM of a pore, illustrating a wide pore body and a narrow, constricted connecting channel to another pore. c) Effect of constriction is to delay diffusion out of pore, due to many "dead" end attempts. Adapted from Reference [8] with permission.

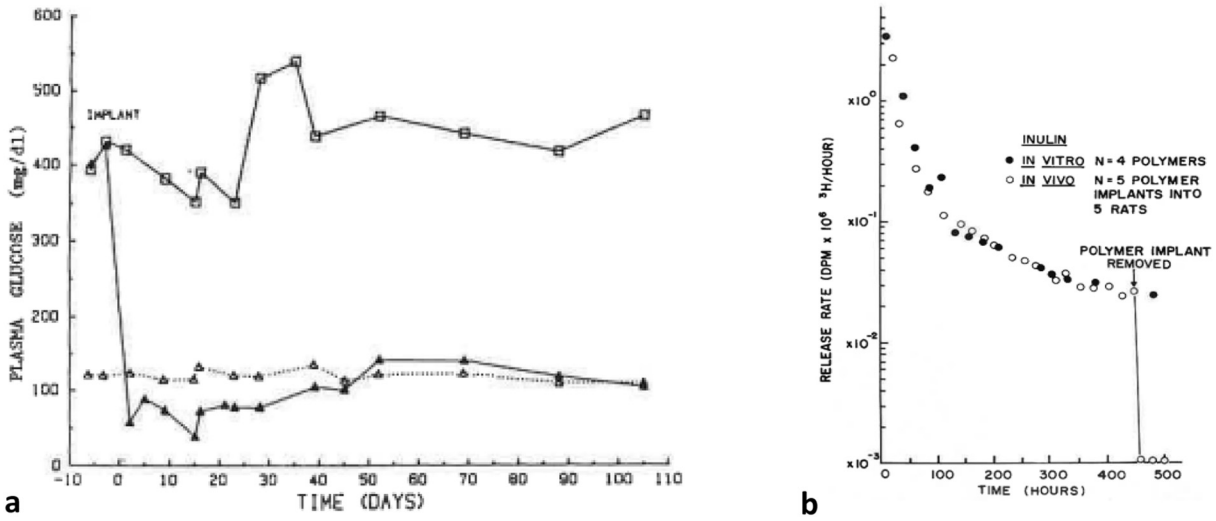

Fig. 2. a) Demonstration of excellent blood glucose control in diabetic rats following implantation of an insulin-loaded EVAc polymer matrix. Open triangles: nondiabetic rats. Open circles: diabetic rats without treatment. Filled triangles: diabetic rats treated with insulin-loaded polymer. Reproduced from [16]. b) *In vitro-in vivo* correlation of release rates of inulin from EVAc. Reproduced from Reference [18] with permission.

photos revealed a porous carcass (Fig. 1a). Evidently, release was occurring through interconnected water channels leading from the inside of the matrix to the outside release medium. In other studies, William D. Rhine et al. [7] showed that release was diffusion controlled, and unlikely to be due to osmotic rupturing of the polymer matrix.

Puzzles remained, however. If release was through water channels, then why was release so slow? Based on the size of the matrices and the diffusion coefficients of globular proteins in water, one would predict release to be essentially complete within a few hours, yet release could persist for months. Classically, retardation of diffusion in porous media was characterized by a "tortuosity" parameter, which referred to the increased effective path length that molecules would have to take due to the structure of the medium through which they diffused. However, for most "reasonable" media, tortuosity by itself could not account for the slowness of release observed from the EVAc matrices.

To address this problem, Ron Siegel carried out a series of release studies in planar slab matrices, with varying loadings and particle sizes of the protein powder. Bovine Serum Albumin (BSA) was used as a model protein. At low loadings and particle sizes, very little BSA was released. However, as loading was increased, a dramatic upswing in fraction released was observed, with the transition becoming sharper as particle size decreased [8,9]. In physical terms, the transition was due to a "percolation threshold," wherein mutually isolated powder granules became more connected with increasing loading, eventually leading to a "globally connected" network. Dissolved and released BSA particles would leave behind pores through which other BSA molecules could diffuse. It was noteworthy however that the sudden increase in fraction release was not accompanied by a sudden increase in release rate. These observations were in line with percolation theory [10], which predicted that above the percolation threshold, pathways formed by interconnected pores would be tortuous, with many "dead ends" that are explored by diffusing molecules before finding their way to the matrix surface.

A second clue was provided initially by an electron micrograph taken by Bawa, showing that connections between pores were relatively narrow compared to the pore diameters (Fig. 1b). These constrictions were, however, much larger than the protein molecules. Using a newly developed Monte Carlo method to simulate diffusion in such constricted porous media [11], it was shown that very large retardations could be accounted for by the difficulty experienced by a randomly diffusing molecule in finding its way out of one pore before it could enter another (Fig. 1c). This was another "dead end" effect occurring at the pore level. The combination of tortuosity and dead end effects inside pores and at the level of the pore network, which was multiplicative, was considered to explain, at least qualitatively, the slow release of BSA observed from the EVAc matrices [12]. More quantitative predictions, using refinements of these ideas, were made later by Mark Saltzmann [13], with considerable success.

5. Controlled release from EVAc *In Vivo*

All the experiments regarding mechanism we carried out *in vitro*, so it was necessary to establish the correlation between *in vitro* release and *in vivo* release. Larry Brown's doctoral work focused on establishing that biologically active proteins such as insulin could be continuously delivered for months in diabetic animals and control blood glucose. Insulin proved to have significantly different physicochemical properties from bovine serum albumin. Albumin's water solubility exceeds 500 mg/mL whereas the commonly available zinc insulin's solubility is < 0.3 mg/mL at pH 7.4. Along with pore structure, solubility strongly influences release rate, as described by the Higuchi equation. Methods were developed to remove zinc from the insulin, yielding a solubility exceeding 100 mg/mL. A mathematical model adapting the Higuchi equation to inwardly releasing hemispheric monolithic ELVAX matrices, which predicted near zero order release [14], was reduced to practice with the zinc-free insulin [15], enabling several months control of blood glucose and significantly improved outcomes for treated diabetic animals (Fig. 2a) [16]. Later, glucose-mediated feedback release was enabled by immobilizing glucose oxidase within the ELVAX matrix. The change in matrix pH in the presence or absence of glucose increased or decreased the insulin solubility and changed insulin release kinetics [17].

Innovative techniques were also developed allowing comparison of *in vitro* and *in vivo* release kinetics from implanted polymers using a radiolabeled polysaccharide, inulin, which is completely excreted into the urine without metabolic transformation (Fig. 2b) [18]. Later, ELVAX protein microsphere fabrication techniques formulations were pioneered [19]. These techniques were later translated into Nutropin Depot (human growth hormone), which became the first high molecular weight biologically active sustained release PLGA microsphere drug product approved by the FDA [20].

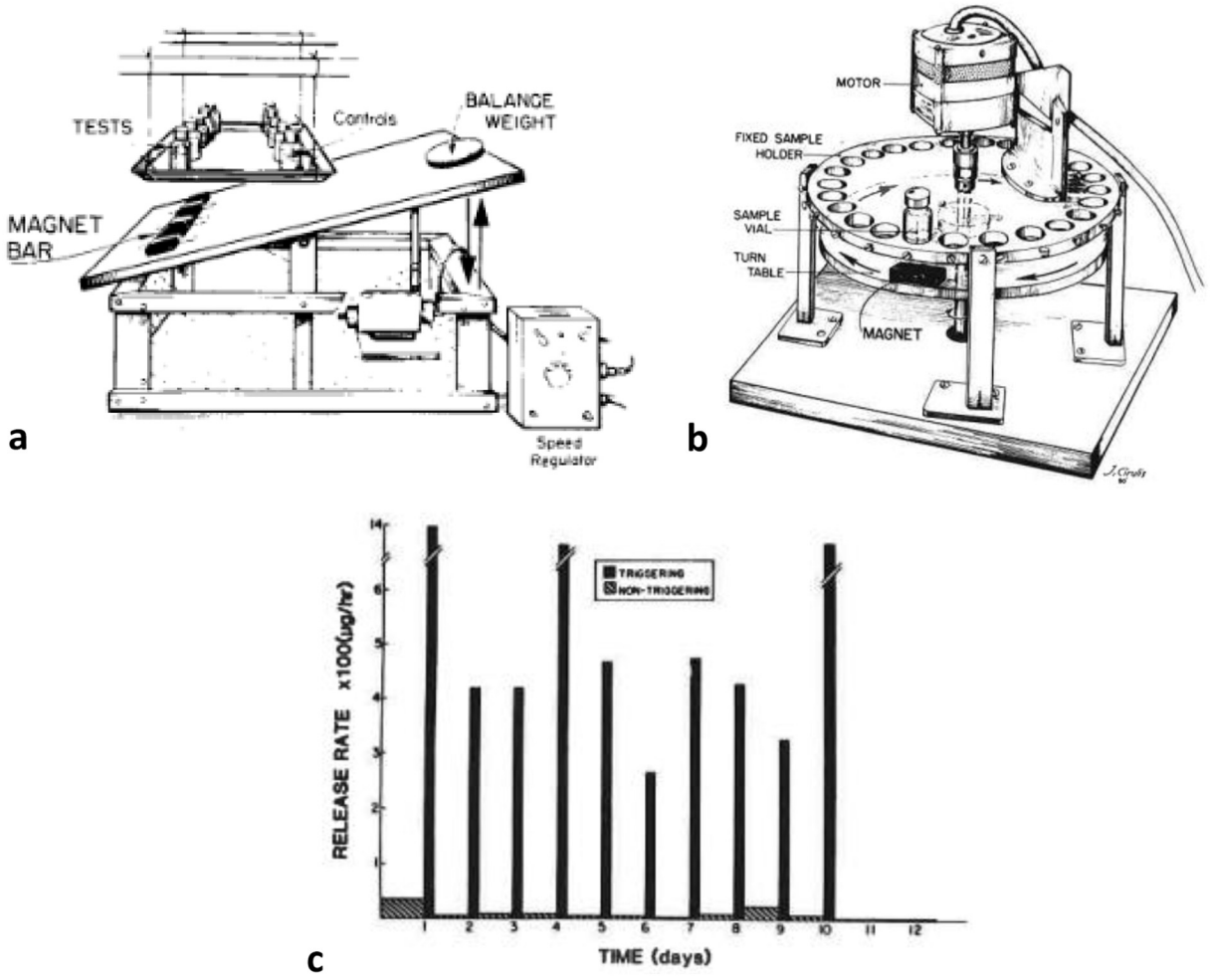

Fig. 3. Magnetic modulation of BSA release from EVAc polymers. Modulation was produced first a) by a permanent magnet mounted on a rocker mechanism and later b) by having the magnet, mounted on a turntable, pass repetitively below the polymer. c) Modulated release rates observed using the turntable mechanism. Hatched bars: turntable off. Solid bars: turntable on. a) reproduced from Reference [21] with permission; b) and c) reproduced from Reference [8] with permission.

6. Magnetic modulation of drug release from EVAc

Very early on, Bob Langer realized that there was a limitation to open, *sustained* drug delivery. Modulation of insulin release in response to changes in glucose level, as discussed above, provided an immediate example of the need for *controlled release*. While similar ideas were being introduced in anesthesia, *e.g.* automatic titration of blood pressure, cardiac output, and heart rate drugs in response to electrophysiological signals, their applications were primarily in acute surgical environments. Could we develop a chronically implanted EVAc system that would respond to an external stimulus, enabling modulated, or triggered drug release?

The first attempt in this direction, carried out by Dean S.T. Hsieh, was to cast magnetic beads, along with the powdered drug, into EVAc matrices [21]. The matrices were then placed in vials containing release media, which were positioned above a seesaw device that lifted and lowered a bar magnet toward and away from the matrices (Fig. 3a). During this seesaw motion, release rate was nearly double that observed in the absence of the modulated magnetic field. A constant magnetic field did not cause a change in release rate, however. Much stronger modulation was produced by Elazer Edelman, who mounted the vials above a cannibalized record turntable, with two ferromagnetic bars secured on the disk (Fig. 3b,c). By this means, it was possible to control the frequency (2×33 1/3, 45, and 78 RPM!) of magnetic modulation, which occurred as the magnets passed under the vials, and substantially stronger modulation was obtained [22]. The mechanism for release modulation was considered to be due to rhythmic squeezing of the pores [23]. Another means of external modulation of release from EVAc, ultrasound was studied by Joseph Kost, who also applied it to bioerodible polymers and to transdermal delivery [24,25].

7. Improved biodegradable polymers for drug delivery

In 1980 there were a limited number of hydrophobic biodegradable polymers for use in drug delivery applications. Of these only polymers containing lactic acid and glycolic acid (PLGAs) were approved, although others, such as the poly(orthoesters) were being developed. Unfortunately, the PLGAs underwent bulk erosion, and tended to release drug with an initial burst of drug incorporated near the surface, followed by a latent period, and terminating with delayed release occurring due to auto-accelerated degradation of the core. Bob Langer asked if there was not a way to design, *de novo*, a hydrophobic biodegradable polymer that would undergo surface erosion to afford zero-order drug release. Bob Linhardt suggested poly(anhydrides), a class of polymers that largely excluded water but contained groups that could react with water at the surface. These polymers could be prepared from hydrophobic diacids. Linhardt and Howard Rosen explored their synthesis and patentability [26]. This work was continued by Kam Leong and Cato Laurencin, among others. Working from first principles, the Langer lab developed the platform technology that lead to the Gliadel® wafer, successfully used to treat brain cancer.

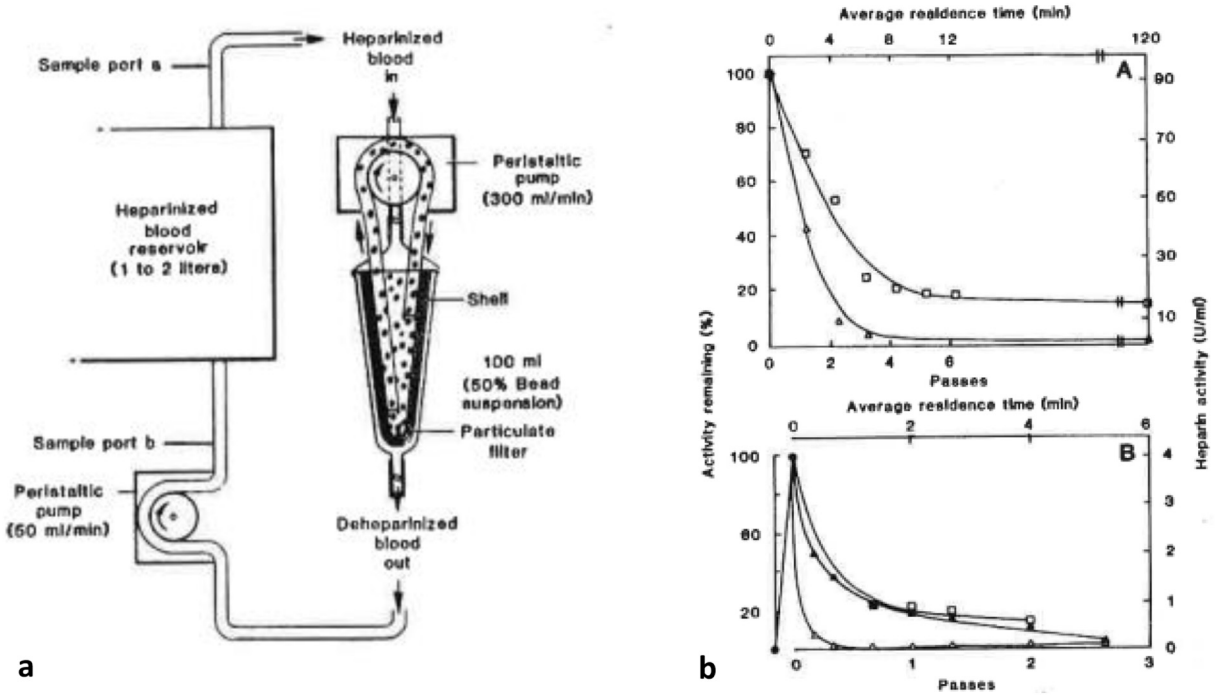

Fig. 4. a) Schematic of the heparinase reactor. b) Performance of the heparinase reactor *in vitro* (top) using heparized human blood, and *in vivo* (bottom), in a cannulated heparinized canine model. Reproduced from Reference [27] with permission.

8. A Heparinase reactor

In addition to drug delivery, Bob Langer was interested in the complementary problem of drug removal. During his collaboration with Judah Folkman, he came to understand that uncontrolled bleeding ranked among the greatest of surgeons' fears. Heparin, a widely used blood anticoagulant, was required for extracorporeal therapy and many medical procedures ranging from kidney dialysis to open-heart surgery. The problem Langer recognized was that this vitally important drug was difficult to remove from the body when uncontrolled bleeding was encountered. Heparin could only be removed or neutralized through whole body blood replacement or the use of protamine, a positively charged mixture of proteins/polypeptides prepared from salmon sperm. Needless to say, these solutions caused their own problems. Langer's solution was to use a bacterial enzyme, heparinase, immobilized in a bioreactor to remove heparin from the extracorporeal circuit. He applied for a grant from the National Institutes of Health that was immediately funded, and Bob Linhardt led this effort. This multifaceted project involved heparinase formation and purification, enzyme immobilization (a recently developed technique), reactor design, and *in vivo* studies (Fig. 4) [27]. A similar reactor for removal of bilirubin was later pursued [28].

9. What became of this work?

We believe it is fair to characterize the work of Langer Labs to be “fundamental applied biomedical research.” The work in the early years laid the groundwork for many advances, which have percolated into the drug and biotech industries, in predictable and unpredictable ways. The ELVAX-40 system for releasing proteins was just a model. Non-degradable polymers such as EVAc are limited in their desirability due to the need for surgical retrieval after use. On the other hand, biodegradable microsphere systems such as Lupron Depot were developed to release peptide gonadotropins over periods of months.

Thin monolithic films have also found applications in releasing drugs from coated cardiovascular stents and pacemaker leads, tamping down proliferative and inflammatory responses to invasive solid materials. Remarkably, ideas behind the coated stent technology can be traced back to a paper published by the Langer group in 1985 [29], and in a short 15 years the power of drug-eluting stents was demonstrated [30].

Work with encapsulated release of growth factors led to the first demonstration of how controlled release could enhance angiogenesis [31,32]. The first demonstration of *in vivo* effects of antisense oligonucleotides [33] provided deep physiologic insights into how biological effects rely substantially on how agents are presented to their targets, and led the way for the explosion in consideration of modified molecular forms from gene therapy to microRNAs. Moreover, the localized release of growth factors has made a strong impact on wound healing and bone repair.

As indicated earlier, the arrival of recombinant proteins was thought to herald a new age of therapeutics. However, initial successes with human insulin and growth hormone were followed by a long gestational period, during which the properties and problems associated with protein drugs came to be better understood. For example, *in situ* protein stability problems were not properly understood. PEGylation allows proteins to circulate for long time periods, lessening the need for implants, although concerns regarding immunogenicity have arisen in recent years. Since about 2000 there has been resurgence in proteins as drugs. Monoclonal antibodies (mabs) now dominate the list of highest selling drugs. In addition to their intrinsic therapeutic properties, mabs are being investigated as carriers of potent small molecule drugs.

Modulated drug delivery remains an interest. During the 1990s, Bob Langer's lab started an effort in using advanced microfabrication (MEMS) techniques to release drugs from microchips at precise times, giving rise the company MicroChips [34]. Superparamagnetic nanoparticles (SNP) have been combined with hydrogels to modulate drug release by external magnetic stimulation [35]. Finally, there is continued interest in systems that modulate drug delivery in response to physiologic signals.

While the heparinase bioreactor was not developed into practical system, the heparinases prepared and characterized resulted in the development of a new low molecular weight heparin, tinzaparin [36], and helped serve as the platform technology for the start-up, Momenta

Pharmaceuticals, Inc. Heparinases have also been used by the medical, pharmaceutical and scientific communities in clinical, medical, pharmaceutical tests and for the studies in basic biology, physiology and pathophysiology. Particularly noteworthy is the application of heparinases in improving the understanding of the basic biology of growth factor signaling [37].

10. Finale

From the start, Bob Langer conducted his research in an unorthodox manner. Trained as a chemical engineer, he could have worked in the petroleum industry, but instead he chosen to work with Dr. Judah Folkman. As a newly minted assistant professor at MIT he reached out for all kinds of expertise, knowing that no single discipline could solve the kinds of problems he was tackling. We four authors came into his lab with training in mathematics, electrical engineering and computer science, biochemistry, medicine, and organic chemistry. We were joined in our work by applied biologists and chemical engineers. Not only did we feel like we were contributing something unique by virtue of our own disciplinary backgrounds, but we were forced to learn from each other in ways that would not occur in labs dedicated to a specific discipline. We have modeled our own careers around this idea that big problems require multidisciplinary solutions.

Acknowledgements

We greatly acknowledge all the people who joined Langer Labs during the period that this essay reports. We were unable to cite all those involved in the projects we described here, and hope that omission of names is not taken as lack of regard. Special thanks to Profs. Edith Mathiowitz and Steven Schwendemann for discussions regarding peptide delivery from microspheres.

References

[1] T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharm. Sci. 50 (1961) 874–875.
[2] J. Wagner, History of pharmacokinetics, Pharmacol. Ther. 12 (1981) 537–562.
[3] K. Itakura, T. Hirose, R. Crea, A.D. Riggs, H.L. Heyneker, H. Bolivar, H.W. Boyer, Expression in *Escherichia coli* of a chemically synthesized gene for the hormone somatostatin, Science 198 (1977) 1056–1063.
[4] D.V. Goeddel, D.G. Kleid, F. Bolivar, H.L. Heyneker, D.G. Yansura, R. Crea, T. Hirose, A. Kraszewski, K. Itakura, A.D. Riggs, Expression in *Escherichia coli* of chemically synthesized genes for human insulin, Proc. Natl. Acad. Sci. U. S. A. 76 (1979) 106–110.
[5] R. Langer, J. Folkman, Polymers for the sustained release of proteins and other macromolecules, Nature 263 (1976) 797–800.
[6] R. Bawa, R.A. Siegel, B. Marasca, M. Karel, R. Langer, An explanation for the controlled release of macromolecules from polymers, J. Control. Release 1 (1985) 259–267.
[7] W.D. Rhine, D.S.T. Hsieh, R. Langer, Kinetics of polymeric delivery systems for proteins and other macromolecules, J. Pharm. Sci. 269 (1980) 275–280.
[8] R.A. Siegel, R. Langer, Controlled release of polypeptides and other macromolecules, Pharm. Res. 1 (1984) 2.
[9] R.A. Siegel, J. Kost, R. Langer, Mechanistic studies of macromolecular drug release from porous polymers. I. Experiments and preliminary theory concerning completeness of drug release, J. Control. Release 8 (1989) 223–236.
[10] S. Kirkpatrick, Percolation and conduction, Rev. Mod. Phys. 45 (1973) 574–588.
[11] R.A. Siegel, R. Langer, Mechanistic studies of macromolecular drug release from porous polymers. II. Models for the slow kinetics of drug release, J. Control. Release 14 (1989) 153–167.
[12] R.A. Siegel, R. Langer, A new Monte Carlo approach to diffusion in constricted porous geometries, J. Colloid Interface Sci. 109 (1986) 426–440.
[13] M. Saltzman, R. Langer, Transport rates of macromolecules in known porous geometries, Biophys. J. 55 (1989) 163–171.
[14] D.S.T. Hsieh, W.D. Rhine, R. Langer, Zero-order controlled release polymer matrices for micro- and macromolecules, J. Pharm. Sci. 72 (1983) 17–22.
[15] L. Brown, L. Siemer, C. Munoz, R. Langer, Controlled release of insulin from polymer matrices. In vitro kinetics, Diabetes 35 (1986) 684–691.
[16] L. Brown, C. Munoz, L. Siemer, E. Edelman, R. Langer, Controlled release of insulin from polymer matrices. Control of diabetes in rats, Diabetes 35 (1986) 692–697.
[17] F. Fischel-Ghodsian, L. Brown, E. Mathiowitz, D. Brandenburg, R. Langer, Enzymatically controlled drug delivery, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 2403–2406.
[18] L.R. Brown, C.L. Wei, R. Langer, In vivo and in vitro release of macromolecules from polymeric drug delivery systems, J. Pharm. Sci. 72 (1983) 1181–1185.
[19] M.V. Sefton, L.R. Brown, R. Langer, Ethylene-vinly acetate microspheres for controlled release of macromolecules, J. Pharm. Sci. 73 (1984) 1859–1861.
[20] OF.L. Johnson, W. Jaworowicz, J.L. Cleland, L. Bailey, M. Charnis, E. Duenas, C. Wu, D. Shepard, S. Magil, T. Last, A.J. Jones, S.D. Putney, The stabilization and encapsulation of human growth hormone into biodegradable microspheres, Pharm. Res. 14 (1997) 730–735.
[21] D.S.T. Hsieh, R. Langer, J. Folkman, Magnetic modulation of release of macromolecules from polymers, Proc. Natl. Acad. Sci. U. S. A. 78 (1981) 1863–1867.
[22] E.R. Edelman, L. Brown, J. Kost, J. Taylor, R. Langer, Modulated release from polymeric drug delivery systems using oscillating magnetic fields: in vitro and in vivo characteristics, Trans. Am. Soc. Artif. Intern. Organs 30 (1984) 445–449.
[23] M.J. McCarthy, D.S. Soong D.S. Mj, E.R. Edelman, Control of drug release from polymer matrices impregnated with magnetic beads - a proposed mechanism and model for enhanced release, J. Control. Release 1 (1984) 143–147.
[24] J. Kost, K. Leong, R. Langer, Ultrasound controlled polymeric drug delivery, Makromol. Chem. Makromol. Symp. 19 (1988) 275–285.
[25] D. Levy, J. Kost, Y. Meshulam, R. Langer, Effect of ultrasound on transdermal drug delivery to rats and guinea pigs, J. Clin. Invest. 83 (1989) 2074–2078.
[26] H.B. Rosen, J. Chang, G.E. Wnek, R.J. Linhardt, R. Langer, Bioerodible Polyanhydrides for controlled drug delivery, Biomaterials 4 (1983) 131–133.
[27] R. Langer, R.J. Linhardt, S. Hoffberg, A.K. Larsen, C.L. Cooney, D. Tapper, M. Klein, An enzymatic system for removing heparin in extracorporeal therapy, Science 217 (1982) 261–263.
[28] C. Sung, A. Lavin, A.M. Klibanov, R. Langer, An immobilized enzyme reactor for the detoxification of bilirubin, Biotechnol. Bioeng. 28 (1986) 1531–1539.
[29] R. Langer, L. Brown, E.R. Edelman, Controlled release and magnetically modulated release systems for macromolecules, Methods Enzymol. 112 (1985) 399–422.
[30] D.E. Drachman, E.R. Edelman, P. Seifert, A.R. Groothuis, D.A. Bornstein, K.R. Kamath, M. Palasis, D. Yang, S.H. Nott, C. Rogers, Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months, J. Am. Coll. Cardiol. 36 (2000) 2325–2332.
[31] E.R. Edelman, E. Mathiowitz, R. Langer, M. Klagsbrun, Controlled and modulated release of basic fibroblast growth-factor, Biomaterials 12 (1991) 619–626.
[32] F.W. Sellke, R.R.R.J. Laham, E.R. Edelman, J.D. Pearlman, M. Simons, Therapeutic angiogenesis with basic fibroblast growth factor: technique and early results, Ann. Thorac. Surg. (6) (1998) 1540–1544.
[33] M. Simons, E.R. Edelman, J.L. Dekeyser, R. Langer, R.D. Rosenberg, Antisense c-*myb* oligonucleotides inhibit intimal arterial smooth muscle accumulation *in vivo*, Nature 359 (1992) 67–70.
[34] J.T. Santini, M.J. Cima, R. Langer, A controlled-release microchip, Nature 397 (1999) 335–338.
[35] X. Zhao, J. Kim, C.A. Cezqr, N. Huebsch, K. Lee, K. Bouhadir, D.J. Mooney, Active scaffolds for on-demand cell and drug delivery, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 67–72.
[36] R.J. Linhardt, A. Grant, C.L. Cooney, R. Langer, Differential anticoagulant activity of heparin fragments prepared using microbial heparinase, J. Biol. Chem. 257 (1982) 7310–7313.
[37] J. Folkman, R. Langer, R.J. Linhardt, C. Haudenschild, S. Taylor, Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone, Science 221 (1983) 719–725.