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# Chronic, programmed polypeptide delivery from an implanted, multireservoir microchip device

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**Implanted drug delivery systems are being increasingly used to realize the therapeutic potential of peptides and proteins. Here we describe the controlled pulsatile release of the polypeptide leuprolide from microchip implants over 6 months in dogs. Each microchip contains an array of discrete reservoirs from which dose delivery can be controlled by telemetry.**

Although oral delivery is a preferred mode of drug administration, the poor oral bioavailability of most therapeutic macromolecules necessitates alternative methods of delivery[1,2]. Existing delivery systems such as polymer depots[3] and osmotic pumps[4] have limited dosing flexibility and may require solution-phase formulations that limit the stability of biological molecules[5]. Here we describe a delivery system that provides precise dosing control (including optional dose termination without device removal) and the flexibility to use solution-phase or solid-phase formulations. Our objective was to use telemetry to regulate the release of a therapeutic polypeptide from a 100-reservoir implant in dogs over a 6-month period. Because the tissue that encapsulates an implant can affect release kinetics, we monitored pharmacokinetics throughout the study.

The nonapeptide leuprolide acetate is an analog of a luteinizing hormone-releasing hormone that is marketed for the treatment of prostate cancer and endometriosis. It was selected as the model drug for this study because it exemplifies therapeutic polypeptides with high potency and poor oral bioavailability that could be of clinical value if delivered through a multireservoir array. In addition, a canine model and bioanalytical methods have been established for the preclinical evaluation of leuprolide pharmacokinetics[6,7].

Microchips were prepared by described methods[8]. Each microchip, measuring 15 × 15 × 1 $mm^3$, contained 100 individually addressable, 300-nl reservoirs (**Fig. 1a**,**b**). This design enabled specific reservoirs to be addressed and opened remotely *in vivo*. In contrast to the electrochemical dissolution approach used previously for release activation[9,10], electrothermal activation opens reservoirs within microseconds in any environment and activation is verifiable[8].

Each reservoir contained about 25 µg of lyophilized leuprolide in a matrix of solid polyethylene glycol (1,450 Da, melting point 42 °C). Individual volumes of the solid-in-solid matrix dosage form were less than 200 nl. Lyophilization was performed on-chip after the reservoirs were aseptically filled with 200 mg/ml of peptide solution (see **Supplementary Methods** for formulation and filling processes). The solid leuprolide dosage form was physically and chemically stable at 37 °C for 6 months (<3% degradation; bioactivity not tested) and showed reproducible pulsatile release kinetics *in vitro* (see **Supplementary Methods** and **Supplementary Fig. 1** online). Reservoirs were aseptically sealed with spheres of indium-tin eutectic solder by thermocompression bonding. Filled and sealed microchips were electrically connected to the wireless communication hardware, power supply and circuit boards of the *in vivo* implant (**Fig. 1c**), which were hermetically sealed inside a laser welded titanium case (**Fig. 1d**). The approximate dimensions of the device were 4.5 × 5.5 × 1 $cm^3$, and its volume was about 30 ml. Straightforward revisions of this design would produce smaller devices with larger dose volumes.

One device (**Fig. 1d**) was implanted into the subcutaneous tissue of each of six male beagle dogs. The capability of the devices for tailoring dose and release timing was demonstrated by varying the number of

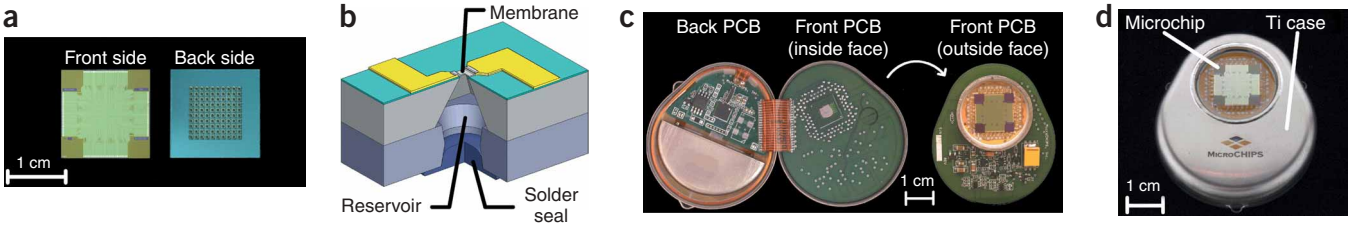


**Figure 1** Images of the microchip reservoirs and implantable drug delivery system. (**a**) Front and back of the 100-reservoir microchip. (**b**) Representation of a single reservoir. (**c**) Electronic components on the printed circuit board (PCB) in the device package. (**d**) The assembled implantable device. **Figure 1d** by Dana Lipp Imaging.

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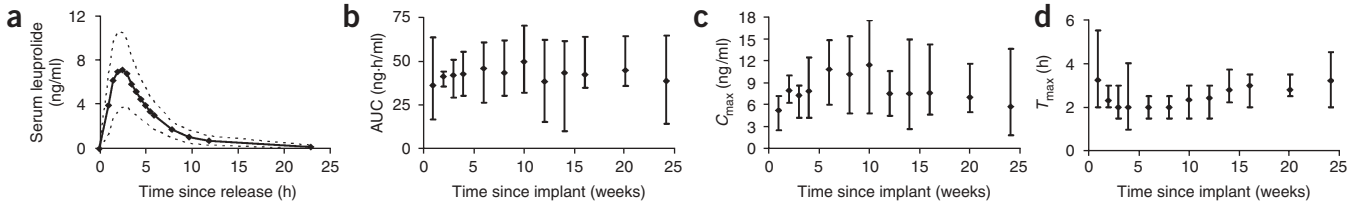


**Figure 2** Summary of *in vivo* results. (**a**) Averaged pharmacokinetic profile for all releases of leuprolide under consideration ($n = 68$). Broken lines represent ± 1 s.d. (**b**–**d**) Average AUC (**b**), $C_{max}$ (**c**) and $T_{max}$ (**d**) for each release event throughout the 6-month study. Vertical lines represent the range of data (weeks 1–12, $n = 6$; weeks 14–26, $n = 5$). Data obtained from one dog-device combination have been excluded after week 14 (see **Supplementary Methods** for details).

reservoirs opened per dose (4–10 reservoirs per release event) and the frequency (every 1–4 weeks) of dosing, beginning 1 week after implantation. The devices were remotely programmed to open selected reservoirs, initiating drug release. Blood was drawn at intervals starting 1 h before and continuing for 24 h after each release activation. Serum leuprolide concentrations were determined by liquid chromatography coupled with tandem mass spectrometry. Measurable release properties were evaluated for statistically significant trends as a function of the study duration (see **Supplementary Methods** for details). Data from the last three release events for one of the dog-device combinations have been omitted from the summary data because detectable amounts of leuprolide began to appear at week 12 in the pre-release blood samples of the dog with this device. In this device, visual and electrical test data were consistent with leakage from the solder seal on the back of the reservoirs. Although this device achieved the objective of peptide release for several months, data obtained from it after week 14 were not representative of a properly functioning device and were excluded from the data analysis (see **Supplementary Methods** for details). We have subsequently developed a biocompatible hermetic sealing method, carried out at temperatures lower than 37 °C, that will increase device reliability.

Serum leuprolide concentrations were normalized to dog weight (10 kg) and leuprolide dose (five reservoir equivalents) to allow inter-dog and inter-week comparisons. The maximum serum leuprolide concentration ($C_{max}$) and area under the pharmacokinetic curve (AUC) scaled linearly with dose size, whereas the time to reach $C_{max}$ ($T_{max}$) was conserved with varying dose. These data, consistent with pharmacokinetic data for the subcutaneous injection of an extended release formulation of leuprolide[6], justify normalizing pharmacokinetic data for the comparison of data obtained at the different doses administered. The mean pharmacokinetic profile, calculated by averaging 68 individual pharmacokinetic curves generated throughout the study period (**Fig. 2a**), was consistent with *in vitro* release kinetics (see **Supplementary Fig. 1** online). The AUC value is indicative of leuprolide bioavailability (**Fig. 2b**), and the $C_{max}$ and $T_{max}$ values provide insight into release kinetics (**Fig. 2c**,**d**).

Within experimental variability, the AUC, $C_{max}$ and $T_{max}$ values of the aggregate data set were constant for 6 months (**Fig. 2a–c**). The averaged AUC values ranged from 37 to 50 (ng·h)/ml (**Fig. 2b**), the averaged $C_{max}$ values ranged from 5 to 11 ng/ml (**Fig. 2c**) and the average $T_{max}$ values ranged from 2.0 to 3.2 h (**Fig. 2d**). Leuprolide bioavailability was estimated at 60% by comparing the AUC data from the aggregate data set (**Fig. 2b**) with AUC data obtained for subcutaneous injections of solution-phase leuprolide, performed before the implant study, and with data for subcutaneously and intravenously administered solution-phase leuprolide in beagle dogs[6] (see **Supplementary Methods** online).

A fibrous capsule, composed primarily of mature collagenous tissue, formed around the implants, as expected[11]. The AUC results (**Fig. 2b**) indicate that the capsule did not significantly affect leuprolide bioavailability. The average $C_{max}$ and $T_{max}$ results (**Fig. 2c**,**d**) indicate that the capsule also did not appreciably affect leuprolide release kinetics (see **Supplementary Methods** for details on statistical treatment of the data).

These encouraging results for leuprolide support the feasibility of applying microchip-based implant technology to deliver other therapeutic peptides and proteins. They also show that drug delivery from an array of discrete reservoirs is not restricted to solution-phase drug formulations and that stability-optimized, solid-phase drug formulations can be packaged and released *in vivo*. To contain efficacious doses, the small volume of the reservoirs used here would require potent drugs. We expect that the incorporation of custom electronic components, biosensors and the further development of techniques for stabilizing concentrated polypeptide formulations will facilitate the delivery of less potent drugs and the creation of smaller implantable devices with enhanced functionality. Future developments will apply this multireservoir device technology to unmet medical needs in the fields of drug delivery and biosensing.

*Note: Supplementary information is available on the Nature Biotechnology website.*

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**COMPETING INTERESTS STATEMENT**

The authors declare competing financial interests (see the *Nature Biotechnology* website for details).

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