ELECTROCHEMOTHERAPY in WIDESPREAD or INOPERABLE CUTANEOUS CANCER

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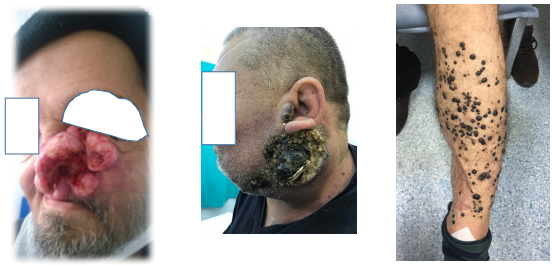
PRIMO JUNE 2019 ISTANBUL

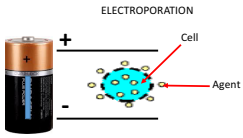
Typical Electrochemotherapy Indications



Electrochemotherapy (ECT) = chemotherapy + electroporation

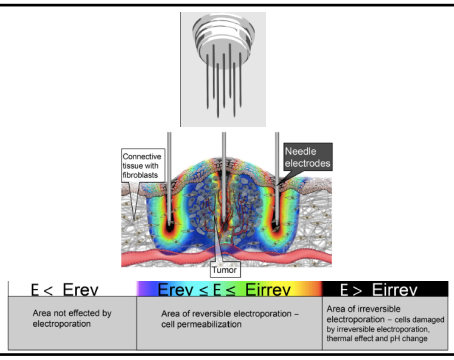
to:

Enhance the intra-cellularization (local) of chemotherapeutics via electroporation

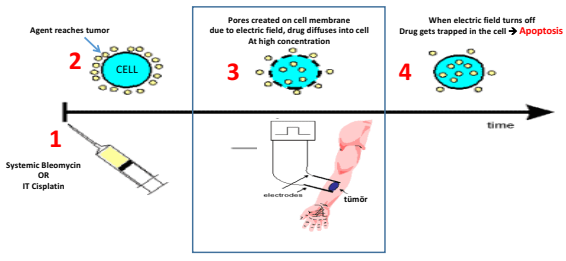


Significance in the Era of Immunotherapy..

- ECT-induced cell death is at least partially immunogenic...
- CR observed only in mice w/intact immune system...
- Works better in patients with history of interferon treatment...



Clinical Procedure



Why Bleomycin?

Bleomycin:

1400gr/mol

15,000UI/m2 dose

Table 1 Summary of drugs tested for *in vitro* and *in vivo* potentiation in combination with electroporation pulses

Drug tested	*In vitro* potentiation	*In vivo* potentiation
Bleomycin	Yes; 100–3000-fold [5,17,18,26–28]	Yes
Cisplatin	Yes; 1.8–12-Fold [17,18,28,29]	Yes [28–30]
Calcium	Yes; more hundred-fold [31,32]	Yes [31]
Netropsin	Yes; 200-fold [1]	–
Carboplatin	Yes; 1.6–13-fold [7,18,27,29]	–
2-N-methyl-9-hydroxy-ellipticinium (NMHE)	Yes; 4-fold [1]	–
Vincristine	Yes; 1.3–3.4-fold [18]	–
ActiNomycin D	Yes; 2–3-fold [1]	–
Cytarabine	Yes; 2-fold [18]	–
Oxaliplatin	Yes [29]	–
Platinum (II) complex 3P-SK	Yes [29]	Yes [29]
Platinum (II) complex PtAMP	Yes [29]	–
Mitomycin C	Yes but low; 1.3–1.4-fold [18,33]	–
Vinblastine	Yes but low; 1.3–1.5-fold [18]	–
5-fluorouracil	No or low; 1.25-fold [18,34]	–
Paclitaxel	No or low; 1.3-fold [7,18]	–
Doxorubicin	No or low; 0.67–2-fold [17,18]	–
Nimustine hydrochloride (ACNU)	No [27]	–
Methotrexate	No [1]	–
9-OH-ellipticine	No [1]	–
Daidmnin B	No [1]	–
Melphalan	No [1]	–
Mithramycin	No [1]	–
Taxotere	No [1]	–
DauNorubicin	No [17]	–
Adriamycin	No [32]	No [28]
Etoposide	No or ND [7,18,27]	–
Anctabine	ND [18]	–
Gemcitabine	ND [18]	–

ND drug was tested but the potentiation could Not be determined due to methodological limitations.

Our (EGE) Electrochemotherapy Team

DR. BURÇAK KARACA

Medical Oncologist

DR. TAHİR GÜRLER

Plastic Surgeon

I. GÖKÇE YAYLA, PhD

Engineer

Kalp pili olan hastaya yüzde lezyon EKT'sinin güvenilir bir şekilde yapılması

ECT centers in Europe

Country	Centres
Italy	37
Germany	45
Austria	2
Portugal	1
Spain	5
Sweden	4
Denmark	1
Greece	2
Switzerland	1
Great Britain/Ireland	12
Hungary	2
Poland	1
The Netherlands	1
Lithuania	1
France	8
Slovenia	3
Belgium	1
Research	12
Total	140

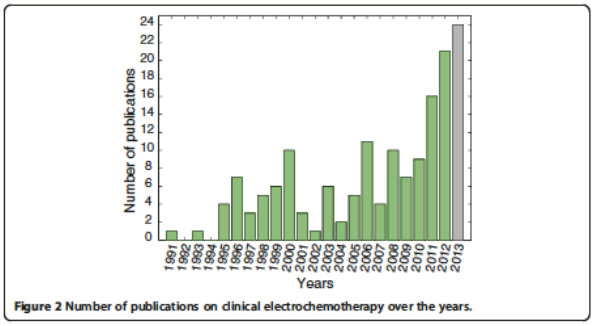
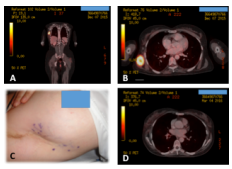


Figure 2 Number of publications on clinical electrochemotherapy over the years.

Table 2 Response rate of the tumors treated by electrochemotherapy, pooled from individual studies

Publication period	No. of studies	No. of patients	No. of tumors	OR (%)	CR (%)	PR (%)	NR (%)
Before SOP	19	175	592	458 (77.4%)[a, b]	362 (61.1%)	96 (16.3%)[c, d]	134 (22.6%)[e, f]
ESOPE	1	41	171	145 (84.8%)	126 (73.7%)	19 (11.1%)	26 (15.2%)
After SOP (Oct 2011)	25	294	1192	1047 (87.8%)[a]	712 (59.7%)	335 (28.1%)[c]	145 (12.2%)[e]
After SOP (Aug 2013)	41	519	1664	1478 (88.8%)[b]	1031 (62.0%)	447 (26.9%)[d]	186 (11.2%)[f]

The studies are grouped in those before, and after the ESOPE study, when the standard operating procedures were published, in 2006. OR = objective response (complete response + partial response); CR = complete response; PR = partial response; NR = no response (no change + progressive disease); [a, b, c, d, e, f] = statistically significant difference ($p < 0.001$, Chi-square test).



Published

Format: Abstract

Full text links

Anticancer Drugs. 2017 Dec 21. doi: 10.1097/CAD.0000000000000560. [Epub ahead of print]

Electrochemotherapy with anti-PD-1 treatment induced durable complete response in heavily pretreated metastatic melanoma patient.

Karaca B[1], Yayla G[2], Erdem M[3], Gürler T[3].

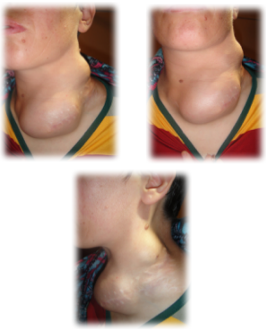
Author information

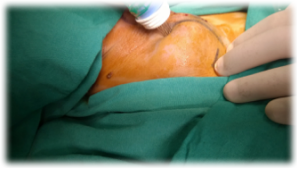
Abstract

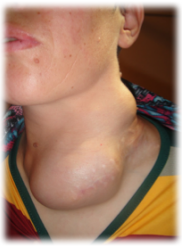
Metastatic melanoma (MM) is one of the most lethal types of cancer. Although novel immunotherapeutics have been developed recently, still, these drugs fail to save the lives of a third of MM patients. Electrochemotherapy (ECT) is a local treatment of cancer based on a combination of electroporesis and low-dose chemotherapy. In this case report, we present the treatment history of a MM patient treated successfully with ECT and immunotherapy combination as a fifth-line treatment. Our patient was a 39 year-old woman who was diagnosed with nodulary melanoma stage II. Due to a local recurrence, she was given interferon-α treatment. After 6 months, her disease relapsed in the axillary lymph nodes, and temozolomide treatment 150 mg/m2 was initiated. After six cycles on temozolamide, she progressed both in the axillary site and in the lungs. Her BRAF mutation analysis revealed V600E positivity. Hence, BRAF inhibitor-vemurafenib 2*4 tablets per day was initiated. Within 3 months, she responded dramatically both in the axillary site and in the lungs. At the ninth month of treatment, she progressed again, at which time ipilimumab 3 mg/kg was started as a fourth line treatment. However, shortly after, she progressed again and developed a solitary brain metastasis. She was operated and had whole brain radiotherapy. At that point, nivolumab, an antiprogrammed cell death ligand-1 blocker, was the only remaining option. She showed a biphenotypical response to nivolumab; a mass on the anterior axilla was progressing while the other lymph nodes had regressed. Owing to the accessibility of the subcutaneous lesion with external electrodes, ECT was performed using IGEA Clinpractor device through a hexagonal electrode on the progressive mass, while on nivolumab treatment. A complete response was achieved, with no evidence of disease at 4 years since her local recurrence. Eradication of symptomatic, refractory lesions using ECT meets an important clinical need. Whenever a disseminated disease presents with cutaneous/subcutaneous lesions, high efficacy of ECT should be deployed to augment tumor immunogenicity and complement systemic immunotherapies.

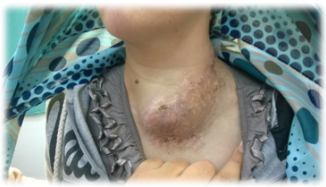
PMID: 29271783 DOI: 10.1097/CAD.0000000000000560

- 38 years, female patient
- Operated at another hospital for neck left sided melanoma 1 year ago.
- Referred to us with a mass on the left side of the neck.

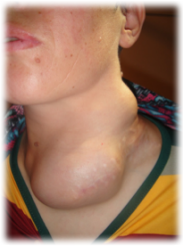


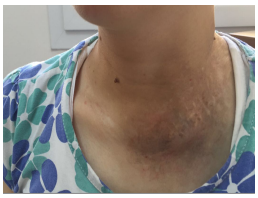




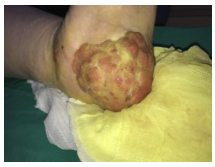


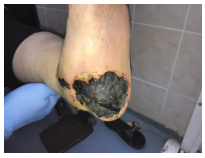
After 3 months



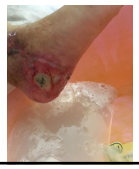


After 1 year

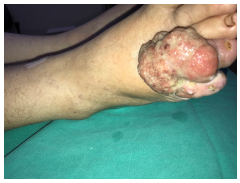


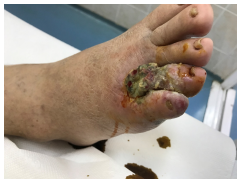


After 3 weeks

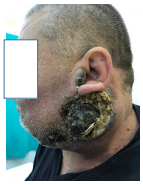


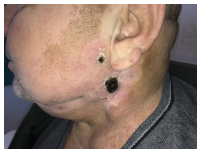
After 2 months



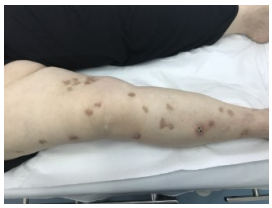


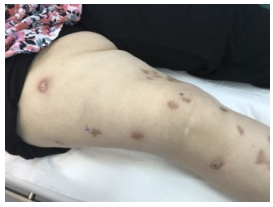
After 1 week



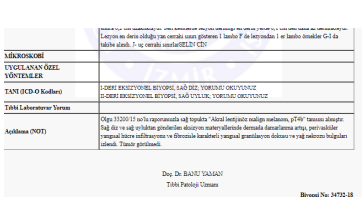


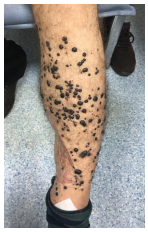
After 1 month

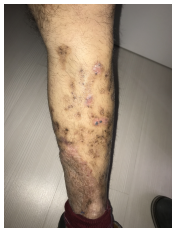




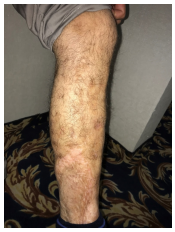
After 6 months



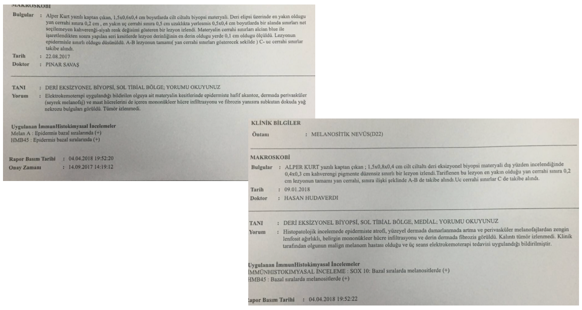




After 3 months



After 1 year



MAKROSKOBİ

Bulgular : Alper Kurt yazılı kaptan çıkan, 1,5x0,6x0,4 cm boyutlarda cilt ciltaltı biyopsi materyali. Deri elipsi üzerinde en yakın oldugu yan cerrahi sınıra 0,2 cm , en yakın uç cerrahi sınıra 0,5 cm uzaklıkta yerlesmis 0,5x0,4 cm boyutlarda bir alanda sınırları net seçilemeyen kahverenği-siyah renk değisimi gösteren bir lezyon izlendi. Materyalin cerrahi sınırları alcian blue ile işaretlendikten sonra yapılan seri kesitlerde lezyon derinliğinin en derin oldugu yerde 0,1 cm oldugu ölçüldü. Lezyonun epidermisle sınırlı oldugu düsünüldü. A-B lezyonun tamamı(yan cerrahi sınırları gösterecek sekilde) C- uc cerrahi sınırlar takibe alındı.

Tarih : 22.08.2017

Doktor : PINAR SAVAŞ

TANI : DERİ EKSİZYONEL BİYOPSİ, SOL TİBİAL BÖLGE; YORUMU OKUYUNUZ

Yorum : Elektrokemoterapi uygulandığı bildirilen olguya ait materyalin kesitlerinde epidermiste hafif akantoz, dermada perivasküler (seyrek melanofaj) ve mast hücrelerini de içeren mononükleer hücre infiltrasyonu ve fibrozis yanısıra subkutan dokuda yağ nekrozu bulguları görüldü. Tümör izlenmedi.

Uygulanan İmmunHistokimyasal İncelemeler
Melan A : Epidermis bazal sıralarında (+)
HMB45 : Epidermis bazal sıralarında (+)

Rapor Basım Tarihi : 04.04.2018 19:52:20
Onay Zamanı : 14.09.2017 14:19:12

KLİNİK BİLGİLER

Öntanı : MELANOSİTİK NEVÜS(D22)

MAKROSKOBİ

Bulgular : ALPER KURT yazılı kaptan çıkan ; 1,5x0,8x0,4 cm cilt ciltaltı deri eksizyonel biyopsi materyali dış yüzden incelendiğinde 0,4x0,3 cm kahverengi pigmente düzensiz sınırlı bir lezyon izlendi.Tariflenen bu lezyon en yakın olduğu yan cerrahi sınıra 0,2 cm lezyonun tamamı yan cerrahi, sınıra ilişki şeklinde A-B de takibe alındı.Uc cerrahi sınırlar C de takibe alındı.

Tarih : 09.01.2018

Doktor : HASAN HUDAVERDI

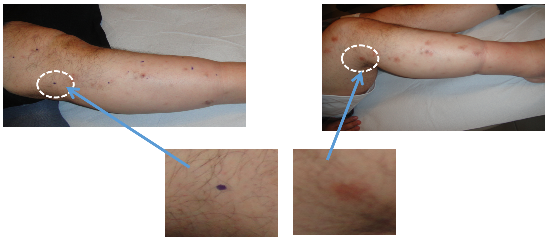
TANI : DERİ EKSİZYONEL BİYOPSİ, SOL TİBİAL BÖLGE, MEDİAL; YORUMU OKUYUNUZ

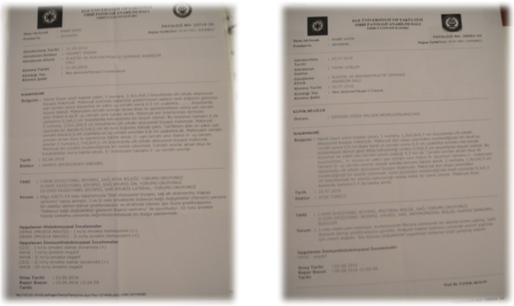
Yorum : Histopatolojik incelemede epidermiste atrofi, yüzeyel dermada damarlanmada artma ve perivasküler melanofajlardan zengin lenfosit ağırlıklı, belirgin mononükleer hücre infiltrasyonu ve derin dermada fibrozis görüldü. Kalıntı tümör izlenmedi. Klinik tarafından olgunun malign melanom hastası olduğu ve üç seans elektrokemoterapi tedavisi uygulandığı bildirilmiştir.

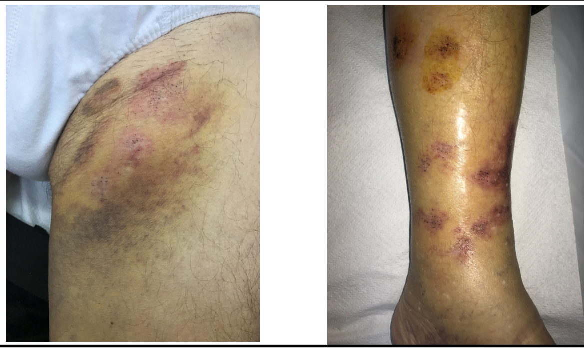
Uygulanan İmmunHistokimyasal İncelemeler
İMMÜNHISTOKIMYASAL İNCELEME : SOX 10: Bazal sıralarda melanositlerde (+)
HMB45 : Bazal sıralarda melanositlerde (+)

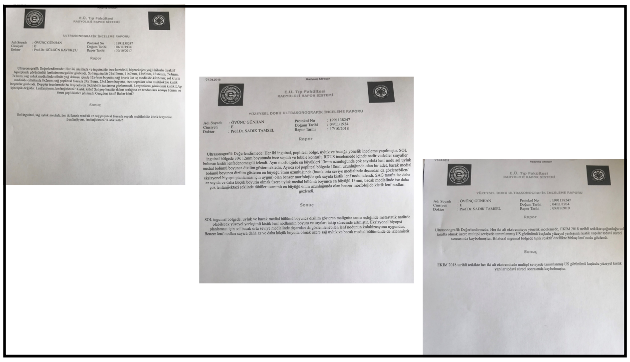
Rapor Basım Tarihi : 04.04.2018 19:52:22

HS, 55, M, Kaposi Sarcoma

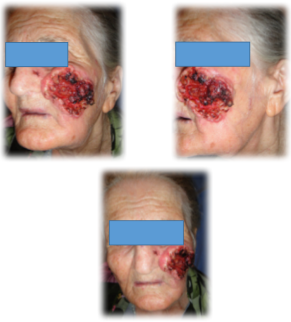


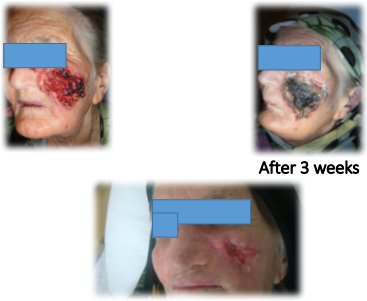


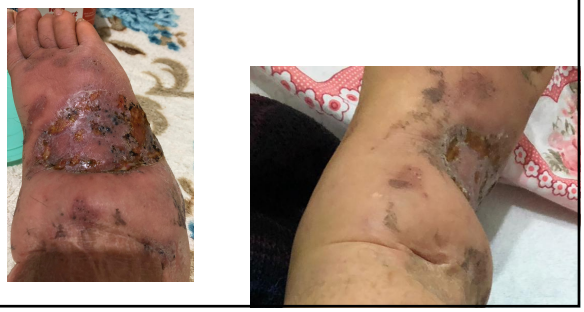


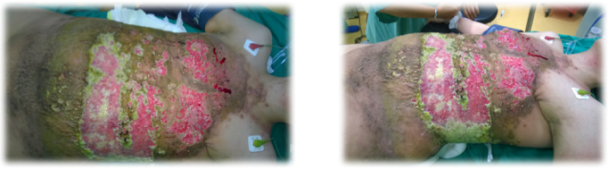


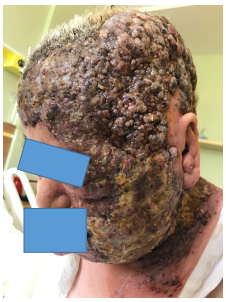
- 82 years, female
- Ulcerous wound at left malar area in three years of time.
- SCC (well differenciated)
  - Treated with several destructive therapies at other centers.
- Referred to us with a left malar mass.
- ECT was applied,
  - Recommended surgery had been denied by the patient.











Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma.

Theurich S[1], Rothschild SI[2], Hoffmann M[3], Fabri M[3], Sommer A[3], Garcia-Marquez M[4], Thelen M[4], Schill C[3], Merki R[5], Schmid T[5], Koeberle D[6], Zippelius A[7], Baues C[8], Mauch C[3], Tigges C[9], Kreuter A[9], Borggrefe J[10], von Bergwelt-Baildon M[11], Schlaak M[12].

Author information

Abstract

Immune checkpoint inhibition with ipilimumab has revolutionized cancer immunotherapy and significantly improved outcomes of patients with advanced malignant melanoma. Local peripheral treatments (LPT), such as radiotherapy or electrochemotherapy, have been shown to modulate systemic immune responses, and preliminary data have raised the hypothesis that the combination of LPT with systemic immune checkpoint blockade might be beneficial. Clinical data from 127 consecutively treated melanoma patients at four cancer centers in Germany and Switzerland were analyzed. Patients received either ipilimumab (n = 82) or ipilimumab and additional LPT (n = 45) if indicated for local tumor control. The addition of LPT to ipilimumab significantly prolonged overall survival (OS; median OS 93 vs. 42 weeks, unadjusted HR, 0.46; P = 0.0028). Adverse immune-related events were not increased by the combination treatment, and LPT-induced local toxicities were in most cases mild. In a multivariable Cox regression analysis, we show that the effect of added LPT on OS remained statistically significant after adjusting for BRAF status, tumor stage, tumor burden, and central nervous system metastases (adjusted HR, 0.56; 95% confidence interval, 0.31-1.01, P = 0.05). Our data suggest that the addition of LPT to ipilimumab is safe and effective in patients with metastatic melanoma irrespective of clinical disease characteristics and known risk factors. Induction of antitumor immune responses is most likely the underlying mechanism and warrants prospective validation. Cancer Immunol Res; 4(9);

Future Oncol. 2017 Aug;13(18):1573-1575. doi: 10.2217/fon-2017-0150. Epub 2017 Aug 22.

Should we be combining local tumor therapies with immunotherapies as standard?

Baues C[1,2], Schlaak M[1,3], von Bergwelt-Baildon M[1,4,5], Theurich S[1,4,6].

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Future?

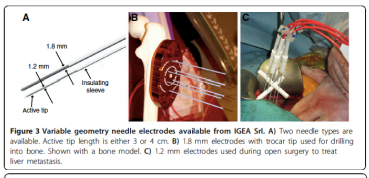
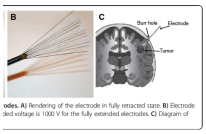


Figure 3 Variable geometry needle electrodes available from IGEA Srl. A) Two needle types are available. Active tip length is either 3 or 4 cm. **B)** 1.8 mm electrodes with trocar tip used for drilling into bone. Shown with a bone model. **C)** 1.2 mm electrodes used during open surgery to treat liver metastasis.



odes. A) Rendering of the electrode in fully retracted state. **B)** Electrode ded voltage is 1000 V for the fully extended electrodes. **C)** Diagram of

Figure 4 Endoscopic electrode EndoVe. A) CAD model. **B)** Photography of an actual sample – recommended voltage 1000 V. **C)** View of the target lesion during endoscopic procedure.

Electro-Gene Transfer

THANK YOU