RETINOBLASTOMA: FROM DIAGNOSIS TO TREATMENT

Doris Hadjistilianou
Ocular Oncology Unit and Retinoblastoma referral center
University of Siena
The retinoblastoma trip… through science, experience, research and clinics
Boston, March 2019
The Rb1 gene…. T. DRYIJA-pioneer in human genetics, 1984

The Rb1 gene....tumor suppressor gene

Predisposes to:
Retinoma
Unil retinoblastoma
Bil retinoblastoma
Osteosarcoma - sec tumors
Trilateral retinoblastoma - Pinealoblastoma
The term “retinoblastoma” dates back to 1926, when it was suggested by Verhoeuff after about 100 years of confusing terminology (Verhoeuff and Jackson 1926), and refers to its development from primitive precursor cells of the retina.
Your Committee now recommends that the term "retinoblastoma" be hereafter used to designate the tumors heretofore designated as glioma of the retina, gliosarcoma, medullary cancer of the retina, neuro-epithelioma retinae, retinocytoma, etc.

The term "retinoblastoma" was suggested by Verhoeff, preferred by Feingold, has been recommended as most appropriate by Cushing and Bailey, and is now the choice of the members of this Committee. It is distinctive, fits in with every known fact
The Golden Age of Eye Pathology

Figure 4. Verhoeuff-Zimmerman Society coat of arms. Note the microscope at the top, 2 hands fighting about a glass slide, 3 X's denoting the 3 originators of the society (Ted Sanders, John McLean, and Benjamin Rones), slide of uveal melanoma, microscope, and motto “Ex Errato Lux” (we learn from our mistakes).

Editorial

Ophthalmic Pathology: History, Accomplishments, Challenges, and Goals
Hans E. Grossniklaus, MD - Atlanta, Georgia
Retinoblastoma histopathology: FREDERICK JACOBIEC
Starting with Retinoblastoma in Siena…

Bonn 1958

The first Xenon
photoacoagulator in Siena

Archives of Ophthalmology 1963

Sarcoma Following Irradiated Retinoblastoma

Report of a Case

A previous paper from this Clinic reported a case of irradiated sarcoma in a child treated at the age of one year by irradiation of the fast-killed tumor, the right, with the Bonn-Xenon photocoagulator in 1958. The left eye, which was anteriorly invaded by the tumor, was treated by irradiation. The xenon photocoagulator was also irradiated anteriorly by the tumor, the treatment was classified as successful with complete regression of the tumor in the remaining eye, and a residual vision of 1/20 for three years.

The patient has now developed a sarcoma in the left visual field since treatment of the radiation of sarcoma in 1958, the majority of case reports have been interpreted as metastatic sarcoma.

Retinoblastoma sarcoma is a rare complication which may occur in any irradiated site. Some reported sarcomas arise in tissues adjacent to the irradiated site but in our case the sarcoma developed in a large area of the right eye, a long time after the tumor had been irradiated.

The purpose of this communication is to present a further case of such a rare complication.

Report of Case

At the age of one year the child was admitted to the pediatric clinic at the Bonn University Hospital. The boy was treated for retinoblastoma in the right eye with the Bonn-Xenon photocoagulator. The tumor regressed for a period of eight months, but subsequently recurred and rapidly grew. The child was referred to the University Eye Clinic at the age of one year. The right eye had a visual acuity of 1/20 and the left eye was blind. The tumor was fixed and did not move with eye movements. The patient was admitted to the University Eye Clinic on March 19, 1963. The sarcoma was removed by enucleation.

The histopathologic examination revealed a flesh-colored mass showing the features of a retinoblastoma and a sarcoma was performed. The excised tissue was fixed in formalin and stained with hematoxylin and eosin. The tumor was histologically characterized by a mixture of retinoblastoma and sarcoma.
40 years of collaboration....

LINIQUE OPHTALMOLOGIQUE
UNIVERSITAIRE
HÔPITAL OPHTALMOLOGIQUE
FONDATION AIGLE ROSE AVENUE
1004 LAUSANNE, la
15, rue de Prémence
Tel: 22 53 52

Monsieur le Professeur Dr. FREZZOTTI
Clinique ophtalmologique de et à
S I E N N E

Concerne: MÊME Fabio TOGNONI - 1.11.1973

Monsieur et cher Confrère,

Les parents du petit Fabio nous ont consultés les 26 et 27 mars pour connaître notre avis sur la nécessité d'énucléer son oeil gauche.

Nous n'avons pas eu la possibilité de procéder à un examen détaillé sous narcose, mais nous avons pu faire un examen à la lampe à fente et une ophtalmoscopie indirecte. Ces examens confirment en tous points vos observations. Nous pensons qu'il s'agit effectivement d'un rétinoblastome bilatéral, compliqué à gauche d'un décollement total de la rétine.

Nous avons insisté auprès des parents pour qu'ils suivent vos propositions, à savoir une énucléation sans tarder de l'œil gauche et nous proposons de tenter un traitement de radiothérapie au Bétaïon pour l'œil droit.

Restant à votre entière disposition pour tous renseignements complémentaires, nous vous prions de croire, Monsieur et cher Confrère, à l'expression de nos sentiments les meilleurs.

Docteur Cl. Gailloud, MD
Médecin-adjoint

Docteur J. Geinoz,
Chef de clinique

27 mars 1975
Retinoblastoma is a rare eye tumor of childhood that arises in the retina and represents the most common intraocular malignancy of infancy and childhood.
Each year, approximately 9000 new cases develop worldwide. RTB is a disease of infants and toddlers, with 95% of cases occurring before the age of 5 years.
Retinoblastoma: diagnosis

RTB can be:
unilateral, bilateral, trilateral

unifocal, multifocal

sporadic, hereditary, within 13q del syndrome

metachronous (occurs in only 1.5% to 3% of EARLY unilateral cases of RTB).

Neonatal / Late
RTB can be:

- Endophytic
- Exophytic
Signs and Symptoms of Retinoblastoma
Retinoblastoma: diagnosis

Examination under GA

Slit lamp examination
Fundus examination
Tonometry
Photos
US
OCT
Leukocoria is the most common initial clinical sign, seen in 60% to 80% of newly diagnosed children.

Leukocoria is generally identified by a family member as a result of an inadvertent finding on flash photography or during screening.

Although half of all cases of leukocoria will be due to RTB, the differential for this presenting sign is quite broad.

OTHER signs: strabismus, nystagmus, buphthalmos, heterochromia, orbital cellulitis, pseudouveitis.
Retinoblastoma: diagnosis
Retinoblastoma: diagnosis (screening in ROP)
Leukocoria
Retinoblastoma: diagnosis

- Iris Heterochromia
- Buphthalmos
- Pseudouveitis (Masquerade Syndromes)
- Orbital Pseudocellulitis
Retinoblastoma: diagnosis

Leucokoria and buphthalmus

- **IRIS HETEROCHROMIA**

- **BUPTHALMOS/RUBEOSIS IRIS**

- **PSEUDOVEITIS (MASQUERADE SYNDROMES)**

- **ORBITAL PSEUDOCOMIPITIS**
Retinoblastoma: diagnosis

- IRIS HETEROCHROMIA

- BUPTHALMOS

- PSEUDOVEITIS (MASQUERADE SYNDROMES)

- ORBITAL PSEUDOCCELLULITIS
Retinoblastoma: diagnosis

PSEUDOVEITIS (MASQUERADE SYNDROMES)

**Diffuse infiltrating RTB** is a rare growth pattern that occurs in 1–2% of RTB. This form is the most difficult to diagnose and it can mimic an inflammatory process.

**Anterior pseudo-uveitis**
Retinoblastoma: diagnosis

PSEUDOUEITIS (MASQUERADE SYNDROMES)

Anterior pseudo-uveitis

- pseudohypopion, hyphema, iris infiltrates
Retinoblastoma: diagnosis

PSEUDO UVEITIS (MASQUERADE SYNDROMES)

Anterior pseudo-uveitis

late or advanced cases
Retinoblastoma: diagnosis

PSEUDOVEITIS (MASQUERADE SYNDROMES)

Anterior pseudo-uveitis
Flocculi and endothelitis in unilateral RTB (8-y old girl)
Retinoblastoma: diagnosis

PSEUDO UVEITIS (MASQUERADE SYNDROMES)

Posterior pseudo-uveitis

Martina, 8 years old girl

RE: Sudden decrease of vision and floaters

First hypothesis: posterior uveitis (Toxocara?)

Referred to us for 2 months later for differential diagnosis
Older children (around 6 years of age) with the diffuse infiltrating variant are more likely to have an unusual presentation, and 1-10% of all the RTB cases present as an inflammatory disease.
Retinoblastoma: unusual patterns

REFERRED TO US: OCTOBER 2016
Treated previously in other institutions with steroids for 6 m
Exam UA:

OD: hyperemia, corneal edema, endothelium alterations
OD: flocculi in the angle
Iris neovascularization and haematic clots (3-10h)
Retinoblastoma: unusual patterns

- **SIENA**: October 2016:

  OD fundus: no retinal masses, torbid vitreous
  Vitreous deposits inferiorly
Retinoblastoma: unusual patterns
Retinoblastoma: unusual patterns
A SECOND OPINION HAS BEEN REQUIRED IN PARIS CURIE INSTITUTE

Retinoblastoma: unusual patterns
RETINOBLASTOMA: UNUSUAL PATTERNS

ANTERIOR CHAMBER TAP
Retinoblastoma: diagnosis

Unusual clinical patterns are typical for RTB in older children

LATE RTB (older children)
Retinoblastoma: diagnosis

- IRIS HETEROCHROMIA
- BUPTHALMOS
- PSEUDOVEITIS (MASQUERADE SYNDROMES)
- ORBITAL PSEUDOCELLULITIS
Retinoblastoma: diagnosis

Orbital pseudocellulitis in trilateral familial RTB

- IRIS HETEROCHROMIA
- BUPTHALMOS
- PSEUDOVEITIS (MASQUERADE SYNDROMES)
- ORBITAL PSEUDOCELLULITIS
Trilateral Retinoblastoma

*Trilateral RTB* is a term referring to bilateral RTB in association with a primary intracranial primitive neuroectodermal tumor.

The intracranial tumor usually occurs within the pineal region, although 25% of cases will have suprasellar tumors.

Trilateral retinoblastoma has had a very poor prognosis.
Retinoblastoma: diagnosis

★ **13q del syndrome**

large low-set malformed ears
high and broad forehead
prominent philtrum
prominent eyebrows
broad nasal bridge
bulbous tip of the nose,
thin upper lip,
micrognathia.

del(13)(q14.1 – q21.1)
Lesions Simulating Retinoblastoma (Pseudoretinoblastoma)

- Coats’ disease
- Retinoma
  - Persistent fetal vasculature
  - Vitreous hemorrhage
  - Toxocariasis
  - Familial exudative vitreoretinopathy
- Rhegmatogenous retinal
- Coloboma
- Astrocytic hamartoma
- Combined hamartoma
  - Congenital cataract
  - Myelinated nerve fibers
  - Endophthalmitis
- Retinopathy of prematurity
- Medulloepithelioma
- X-linked retinoschisis
- Incontinentia pigmenti
- Juvenile xanthogranuloma
- Norrie’s disease
- Vasoproliferative tumor
- Choroidal osteoma
- Morning glory disc anomaly
- Retinal capillary hemangioma
- Retrolental fibrosis
- Toxoplasmosis
Retinoblastoma ????Or what else …..?
Coats disease vs retinoblastoma
Which child has which?

Coats’ disease  xanthocoria  RTB  leukocoria
<table>
<thead>
<tr>
<th>MACULA</th>
<th>VITREOUS</th>
<th>CALIBER</th>
<th>SUBRET. MAT.</th>
<th>ANT. CH.</th>
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*Note: Images not included in the text representation.*
CLINICAL EVALUATION

Size, site, number
Vitreous Seeding focal, diffuse
Seeding subretinal
Anterior segment involvement
Secondary glaucoma

Staging

Optic nerve involvement
Scleral invasion
MRI risk factors
Retinoblastoma: diagnosis
Neonatal retinoblastoma

The very early diagnosis of retinoblastoma does not guarantee early stage of the disease and eye salvage
Vitreous seeding: what it is???

Free-floating buds of tumor cells within the vitreous.

Vitreous seeding is one of the primary reasons for treatment failure following conservative management of retinoblastoma.
RETINOBLASTOMA: DIAGNOSIS

Vitreous seeding:
- Dusty
- Spheric
- Cloudy

Regression:
- Type 0, not visible
- Type I, calcific
- Type II, amorphous
- Type III, mixture of type I and II
What the ophthalmologist should refer to the pediatric oncologist?

- Bil or unil
- Multifocal, unifocal
- Calcifications
- Cystic pattern
- Subretinal seeding
- Vitreous seeding
- Anterior chamber involvement
- Intraocular pressure Sec glaucoma
- Other ocular abnormalities
What the pediatrician and ocular oncologist should ask to the neuroradiologist?

- Infiltration
- Choroid
- Sclera
- Optic nerve (pre or post laminare)
- Calcifications

- Trilaterality
- Pineal cysts
- Orbital RTB
- Metastatic RTB
CLINICAL CRITERIA

Size, site, number
Seeding focal, diffuse
Seeding subretinal, vitreous

Anterior segment involvement
Secondary glaucoma

Optic nerve involvement
Scleral invasion
MRI risk factors

CONSERVATIVE THERAPIES

Staging
### STAGING - ABC classification

#### Stage

<table>
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<tr>
<th>ABC classification</th>
<th>Reference photo</th>
<th>R-E</th>
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<tbody>
<tr>
<td><strong>Group A</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Reference photo" /></td>
<td>Ia, Ib, IIIa, IVb</td>
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<tr>
<td>Small tumor(s) confined to the retina</td>
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<tr>
<td>None higher than 3 mm</td>
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<tr>
<td>None less than 2 DD from fovea or 1 DD from optic nerve</td>
<td></td>
<td></td>
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<tr>
<td>No vitreous seeding or RD</td>
<td></td>
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<tr>
<td><strong>Group B</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Reference photo" /></td>
<td>Ia, Ib, IIIa, IIIb, IVa, IVb</td>
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<tr>
<td>Tumors confined to the retina</td>
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<tr>
<td>Any location</td>
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<tr>
<td>No vitreous seeding or localized vitreous seeds</td>
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<tr>
<td>No RD &gt; 5 mm from tumor base</td>
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<tr>
<td>Fine diffuse vitreous seeding</td>
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<tr>
<td>Retinal detachment &gt; group B to total RD</td>
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<td></td>
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<tr>
<td>Tumors &gt; 15 mm</td>
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<tr>
<td><strong>Group C</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Reference photo" /></td>
<td>IVa, IVb, Va, Vb</td>
</tr>
<tr>
<td>Massive vitreous/ subretinal seeding</td>
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<tr>
<td>Retinal detachment &gt; Group B to total RD</td>
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<tr>
<td>Tumor more than half of the retina</td>
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<tr>
<td><strong>Group D</strong></td>
<td><img src="https://via.placeholder.com/150" alt="Reference photo" /></td>
<td>IVa, IVb, Va, Vb</td>
</tr>
<tr>
<td>No visual potential, OR</td>
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<tr>
<td>Presence of any one or more: Tumor in CB anterior segment</td>
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<td></td>
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<tr>
<td>Nodular glaucoma</td>
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<tr>
<td>Vitreous hema/hage</td>
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<tr>
<td>Phlebal, prephlebal eye</td>
<td></td>
<td></td>
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<tr>
<td>Hyphema/ corneal staining</td>
<td></td>
<td></td>
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<tr>
<td>Orbital cellulitis-like presentation</td>
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<tr>
<td>Tumor anterior to anterior hyaloid</td>
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**STAGING - ABC classification**

- Stage
- ABC classification
- Reference photo
- R-E
Retinoblastoma: Treatment
ENUCLEATION

ORBITAL IMPLANT IN CHILDREN

< 4M  16 mm
4 – 12M  18 mm
12 – 48M  18 – 20 mm
ENUCLEATION GUIDELINES

• Group F, ABC classification
  • Massive Anterior chamber involvement
  • Pseudouveitis in retinoblastoma
  • (masquerade syndrome)
  • Secondary glaucoma, buphthalmus
  • Phtysis bulbi
What pediatrician and ophthalmologist should ask to the pathologist
ADVERSE HISTO-PROGNOSTIC FACTORS:

- Involvement of anterior segment
- Involvement of penetrating arteries
- Involvement of ON at the cut edge
- More than one risk factors

CH±RT
ENUCLEATION GUIDELINES

ENUCLEATION SHOULD BE PERFORMED IN A TERTIARY REFERRAL CENTRE IN ORDER TO:

• Guarantee right enucleation criteria and case eligibility
• Perform a correct enucleation technique (posterior neurotomy and orbital implant)
• Follow the pathology protocol for disease staging
• Harvest material for molecular biology bank
Extraocular Retinoblastoma

The mass was 506 gr and macroscopically similar to brain tissue.
Extraocular Retinoblastoma

The presence of worms was observed in the necrotic part of the tumor.

Undifferentiated Retinoblastoma with massive infiltration of orbit stroma, muscles, skin, underskin and orbital socket.
RELAPSE THREE MONTHS LATER
TWO MONTHS SURVIVAL
Orbital Retinoblastoma: excision + CT + RT
Late diagnosis of unilateral RTB (RE)
2 years later: contralateral orbital and systemic metastasis
CONSERVATIVE THERAPIES

- Focal therapies
  - Argon
  - Dyode (TTT)
  - Cryo
  - Plaques (Ru $^{106}$, I $^{125}$)

- Chemotherapy
  - Cryo
  - Thermo
  - Argon laser

- EBRT

- Local
  - Peri-CH
  - IV-CH
  - IA-CH
MAY, 2008

NEW YORK … WITH
D. ABRAMSON (MEMORIAL)
AND P.GOBIN (CORNELL)
RTB: combining IntraArterial and IntraVitreal Chemo

1954: Reese
1961: Ericson & Rosengren
1968: Kiribuchi
1995: Seregard
2004: Kaneko & Susuki
2010-2011: Munier

IA INTRAARTERIAL Melphalan, topotecan, carboplatin

IV INTRAVITREAL MELPHALAN

2004: Kaneko
2006: Abramson
INTRAARTERIAL CHEMOTHERAPY: 10 ys EXPERIENCE

10 ys EXPERIENCE
2008-2018

180 eyes - 796 procedures
INTRAARTERIAL CHEMOTHERAPY

• Direct ophthalmic artery catheterization
• It is important to note intra-arterial treatment is intended for intraocular retinoblastoma and not for disease with extra-ocular involvement
• The three principal chemotherapeutics used intra-arterially are melphalan, topotecan and carboplatin.
INTRAARTERIAL CHEMOTHERAPY: INDICATIONS

**UNILATERAL RTB (naive)**

- Age > 6 months, weight 7 kg
- Group B → D (excluded macular free eyes)
- Selected E Group
- Relapse / partial response (after conventional therapy)

**BILATERAL RTB (after conventional therapy)**

- Relapse / partial response (worst eye)
- Synchronous relapse
- TANDEM IA
- Partial response in both eyes
Primary vitreous seeding is typically seen in NAÏVE advanced intra-ocular RTB

Secondary vitreous seeding: presence of viable retinoblastoma seeding into the vitreous after IV or IA-CH is a major obstacle to globe salvage
Intraarterial chemo drugs

MELPHALAN
- Dose: 2.5 – 5 mg

TOPOTECAN
Dose: 0.3 – 2 mg

CARBOPLATIN: 30mg

Intravitreal

MELPHALAN
- Dose: 10-30μg

(IA: 3-9 infusions every 3 weeks)
(IVi: 1 injection 1 week after IA)
Sequential intra-arterial and intra-vitreal chemotherapy for naive advanced STAGE D Rtb

OUR EXPERIENCE

2 IA ...... ......8 DAYS ..... Ivi ...... 15 days........IA ............8DAYS.....IVi
SR: unilateral rtb (12m) group D with type 3 clouds seeding

At diagnosis, after 6 IA infusions and 3 IVi injections.

Complication: chorioretinal atrophy

IA-IV SUCCESSFUL TREATMENT

F-up: 5m
MA: Unilateral RTB (3y5m): large endophytic tumor with diffuse vitreous and subretinal seeding.

Ophtalmoscopy after 6 IAC infusions and 4 IViC injections. No complications.
BE: Unilateral RTB (2y10m): group D with type 3 snowball seeding

At diagnosis, after 6 IA infusions and 6 IV injections.
Complication: chorioretinal atrophy
INTRAARTERIAL CHEMOTHERAPY SIDE EFFECTS

Extraocular /early and transient

1. Frontal rash
2. Eyelid edema
3. Hyperaemia,
4. Alopecia
5. Madarosis

Transient side effects are mostly present after the first infusion and less frequent at the following ones.
INTRAARTERIAL VS INTRAVENOUS CH:

Permanent late side effects (RPE ALT, CHOR ATR)

3.2% CHOR ATR
mAge 7 months

22.5% CHOR ATR
mAge 21 months

38.7% RPE ALT
mAge 5 months

19.3% RPE ALT
mAge 23 months
Retinoblastoma - twinning is winning
Siena University Hospital - Aghia Sofia Athens Hospital
In 2016, birth rate for Greece was 8.6 per 1,000 people.

Birth rate of Greece fell gradually from 18.8 per 1,000 people in 1967 to 8.6 per 1,000 people in 2016.

**Greece Population clock (live)**

05-09-2018 22:49:24

10,815,825
Current population

5,352,625
Current male population (49.5%)

5,463,200
Current female population (50.5%)

65,781
Births this year (expecting approx. 80.00)

APPROX 5-6 RTB CASES PER YEAR
RETINOBLASTOMA-SPECIFIC TWINNING PROGRAMME: AGHIA SOFIA ATHENS HOSPITAL – UNIVERSITY OF SIENA

WHAT WE ACHIEVED IN ATHENS:

- improve knowledge
- improve diagnosis and treatment
- improve quality of life
- reduce patients moving
- reduce costs
- create a new team
- create telemedicine
- guarantee permanent mentorship
THANK YOU!!!
THANK YOU!