CURRENT TREATMENT OF AGCT AND FUTURE PERSPECTIVES

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- No conflicts of interest

AGCT

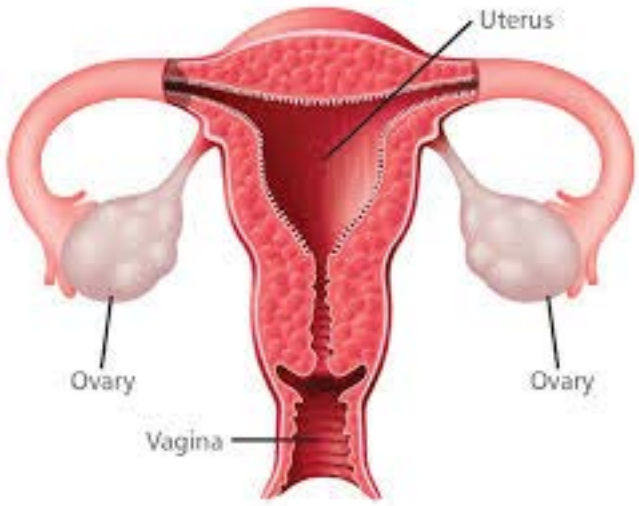
- Prognosis
  - 5-year survival 90-97% in stage I *(Colombo et al 2007, Bryk et al 2015)*
    22-75% in stage II-IV *(Björkholm et al 1981, Fujimoto et al 2001)*

- 30% relapse
  - median time 4-8 years *(Lee et al 2008, Sun et al 2012, Bryk et al 2015)*
  - mortality to recurrent disease 50% *(Bryk et al, unpublished)*

Treatment of AGCT

- Surgery, primary tumor:
  - Laparotomy (open) or laparoscopic surgery
  - Removal of the uterus, ovaries and fallopian tubes, peritoneal washings, biopsies and omentectomy
  - Lymfadenectomy not recommended as routine procedures, suspicious nodes should be removed
  - Tumor rupture is an adverse prognostic factor

    -> centralization of the treatment to specialized units!

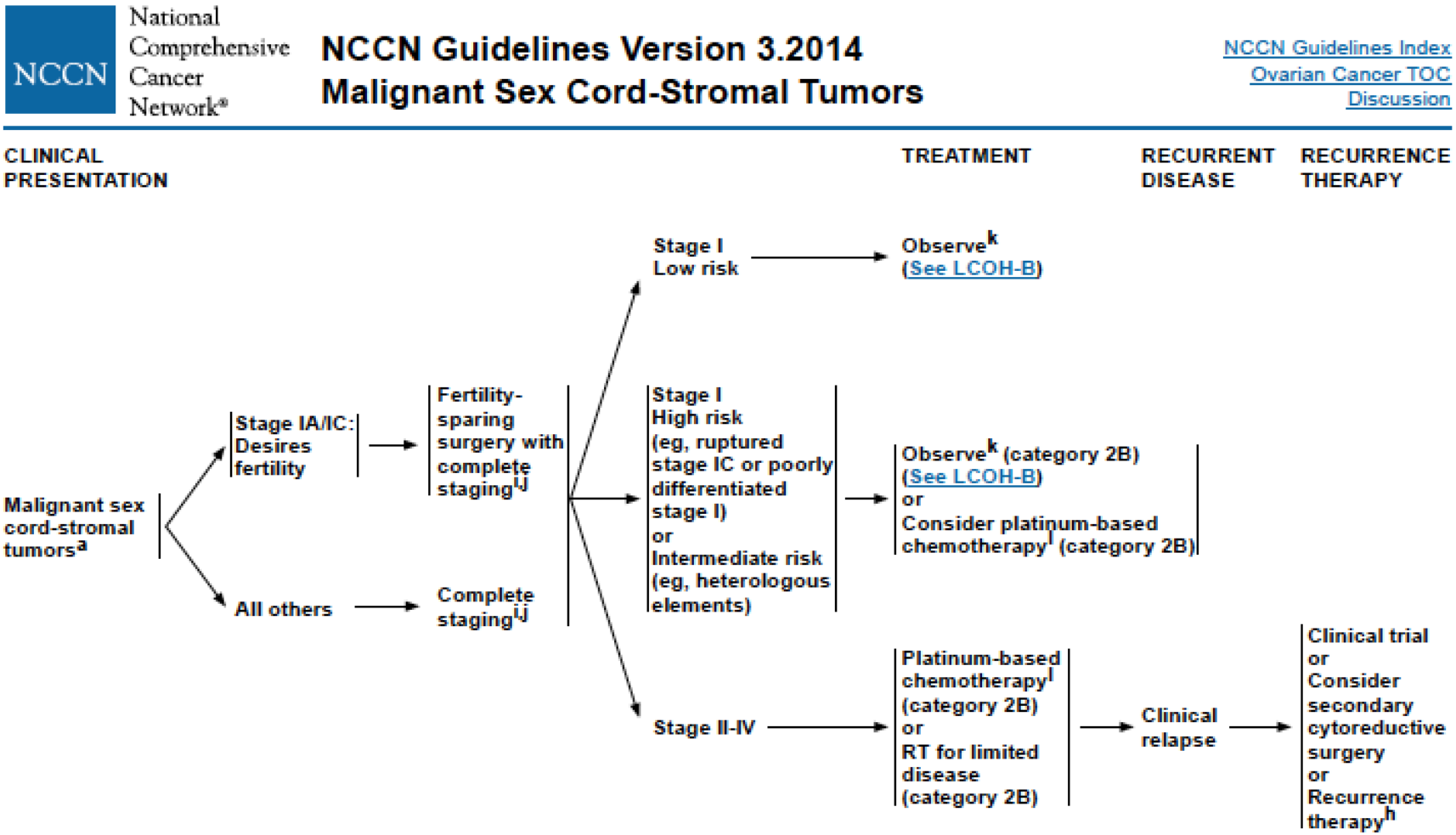


- Fertility-sparing surgery (in stage I (a)): uterus and healthy ovary conserved, biopsies and endometrial sampling should be performed
- Younger age may be associated with relapse
- Long latency to relapse -> No consensus what to do when reaching menopause

Recurrent tumors

- Often multifocal
- Pelvis as the most common site
- Metastasis to distal organs are rare
- Optimal surgery is important
  - Debulking surgery (ESMO guidelines)
  - Even repeated operations (Mangili 2013)
  - Residual tumor is a significant adverse prognostic factor
- Optimal surgery achieved in 71-85 % of the recurrences (Ertas 2014)

Chemotherapy



Chemotherapy

- ESMO guidelines
  - Recommended as adjuvant in stage Ic/II primary tumor or higher and in recurrent AGCT
  - BEP=Bleomycin, Etoposide, Carboplatin (3-6 cycles)
  - other options
    - Etoposide, Cisplatin
    - Cyclophosphamide, Doxorubicin, Cisplatin
    - Paclitaxel, Carboplatin
    - Platinum agent alone
    - PVB (Cisplatin, Vinblastine, Bleomycin)
    - VAC (Vincristine Dactinomycin Cyclophosphamide)

BEP/BEC response rates

Patients	Response rates	Reference
5 (2 res, 3 rec)	2 x CR (40%) 3 x PR (60%)	**Gershenson 1996**
25	6 x CR (24%) 4 x PR (16%) 14 x SD (56%) 1 x PD (4%)	**Homesley 1999**
20 (5 res, 15 rec)	9 x CR (45%) 9 x PR (45%) 1 x SD (5%) 1 x PD (5%)	**Pautier 2008**
9 (9 rec)	**1 x CR (11%)** **1 x PR (1%)** **7 x SD (78%)**	**Van Meurs 2013**

Adjuvant therapy – effect for relapse?

- Park 2012
  - Adjuvant BEP chemotherapy not significantly associated with DFS
  - 6/13 completed 6 cycles of BEP: no recurrence
  - 7 patients received fewer than 6 cycles, 5/7 had recurrences
- Meisel 2015
  - BEP did not improve the recurrence free interval

BEP/BEC adverse effects

- Pulmonary toxicity
  - Bleomycin induced pneumonitis > lung fibrosis
- Skin reactions
- Bone marrow suppression
- Gastrointestinal symptoms

- Cisplatin vs carboplatin

Taxanes

- Brown et al 2005: same efficacy with less toxicity when compared with BEP

- GOG trial ongoing: **Paclitaxel and Carboplatin or Bleomycin Sulfate, Etoposide Phosphate, and Cisplatin in Treating Patients With Advanced or Recurrent Sex Cord-Ovarian Stromal Tumors**

Targeted treatments

- Bevacizumab
  - Angiogenesis inhibitor
  - AGCTs highly vascularized, VEGF elevated in AGCT
  - Brown 2009: Bevacizumab showed activity:response rate 38%
    - 8 GCTs, 1/8 CR, 2/8 PR, 3/8 disease progression
  - Brown 2015: GOG phase II trial, activity in AGCT (PR 16%), toxicity acceptable

  - Adverse effects
    - hypertension
    - proteinuria
    - bowel perforation

Hormonal treatments

- AGCT is a hormone secreting tumor
  - Inhibins, estradiol (E2)
- Drugs
  - Aromatase inhibitors
  - Selective Estrogen Receptor Modifiers (Tamoxifen)
  - Progestins
  - GnRH agonists
- Efficacies :CR 25.8%, PR 45.2%, aromatase inibitors most efficient (van Meurs 2014)
- Recent studies: CR 4,5%, PR 14%, SD 64%, progression 18% (van Meurs 2015)

Future perspectives

- Targeted treatments
  - Less side effects
  - Biological background

- Mechanisms of hormonal modulation

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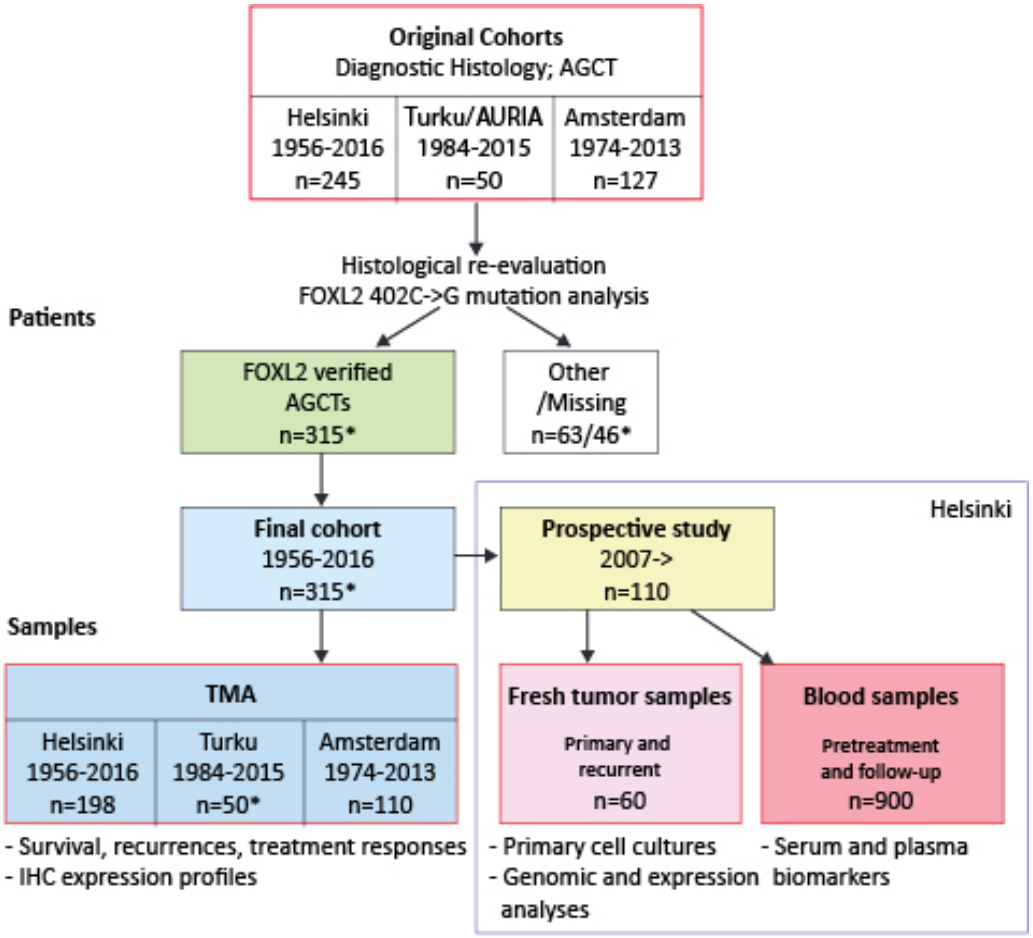
AGCT patients and samples



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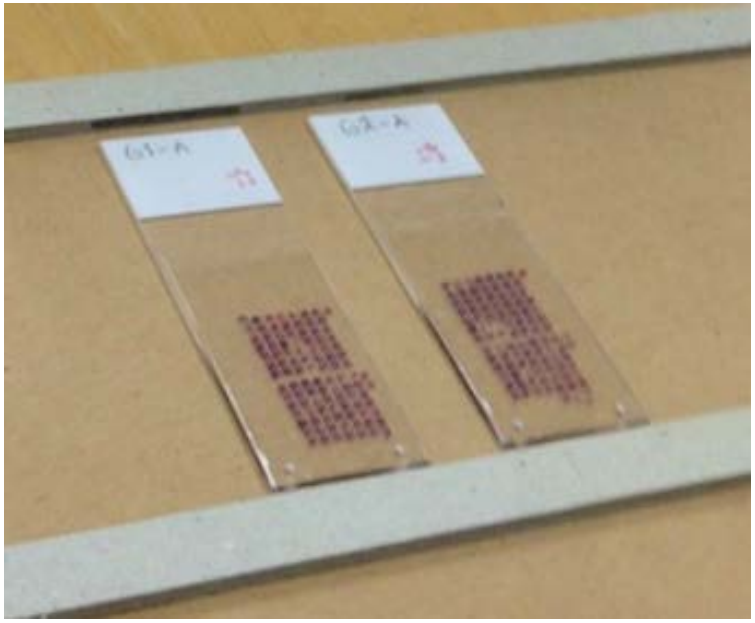
- Clinical and translational studies
  - Comprehensive database
  - Primary GCT cell culture model
  - Fresh AGCT samples
  - GCT cell lines
  - Tumor tissue microarrays
  - Serum samples
- 5-10 new AGCTs every year



Serum markers in AGCT

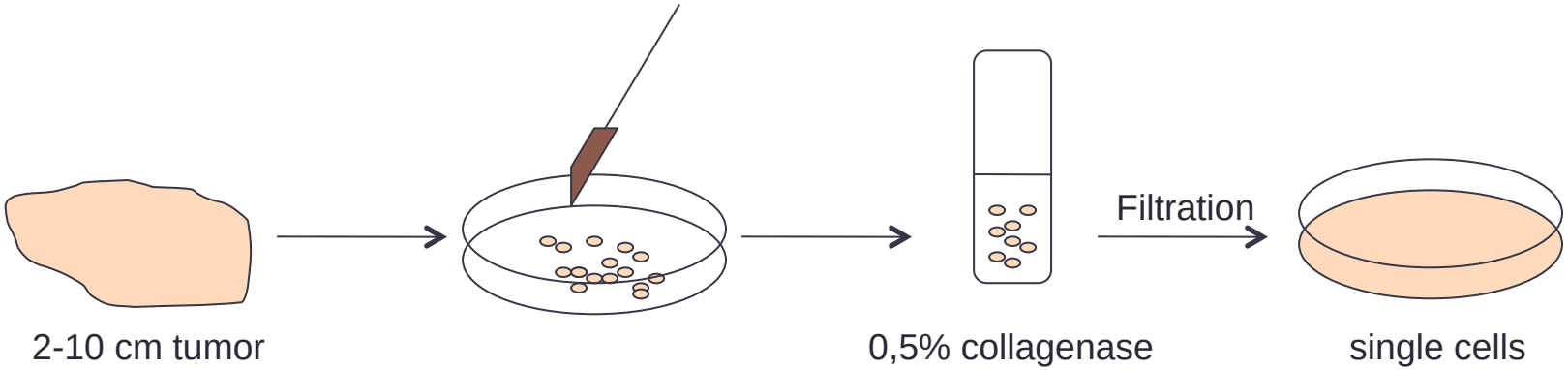
- **Diagnostic markers for patients with Ovarian Granulosa Cell Tumors; comparative analysis of CA125, HE4, Inhibin B and AMH**

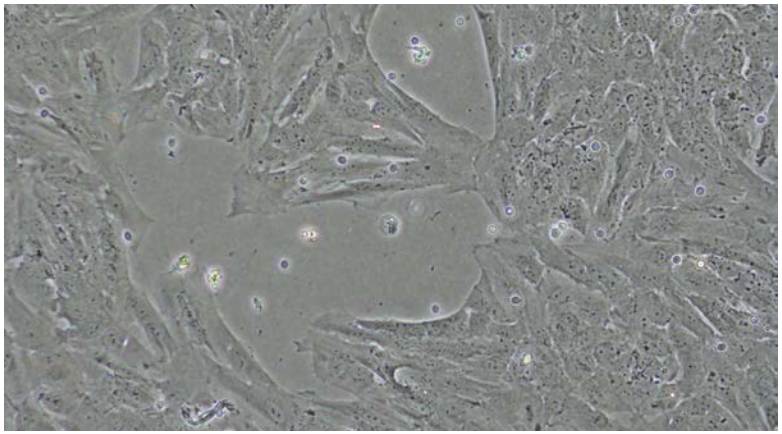
  - CA125 levels usually not elevated in AGCT but no studies on HE4-levels in AGCT
  - Preoperative diagnosis is important
    - Referral of patients to specialized units
  - To find most optimal serum marker/marker combination for AGCT

Conclusion

- HE4 levels are not elevated in AGCT
- Inhibin B is the best marker to differentiate AGCT from both malign and benign ovarian cysts.
- For differentiating AGCT from EOC, Inhibin B alone is sufficient
- For differentiating AGCT from endometriomas, Inhibin B and AMH in combination is most optimal
- In this study, Inhibin B was the best follow-up marker for AGCT

Primary cell cultures of AGCTs



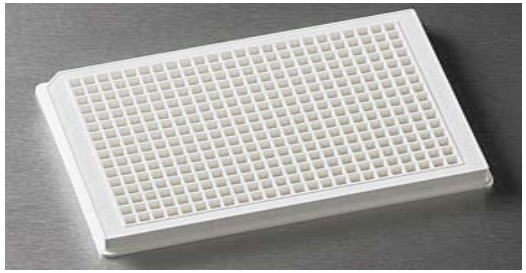


experiments

Drug sensitivity and resistance testing (DSRT)

- Measures how efficiently different drugs inhibit tumor cells
- Over 300 drugs screened at the same time (approved cancer drugs and novel agents)
- Drugs plated on 384-well plates at five different concentrations (from 1 nM to 10 µM)
- Isolated primary cultured GCT

cells added> Incubation for 3 days

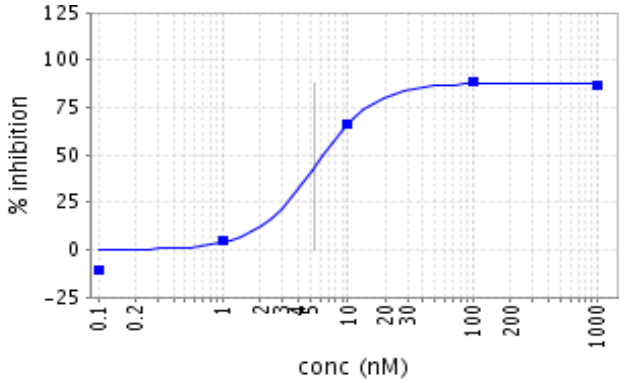


DSRT results

- Drug efficacy measured by the amount of viable (ATP-producing) cells
- IC50-value
  - Required dose to kill 50%

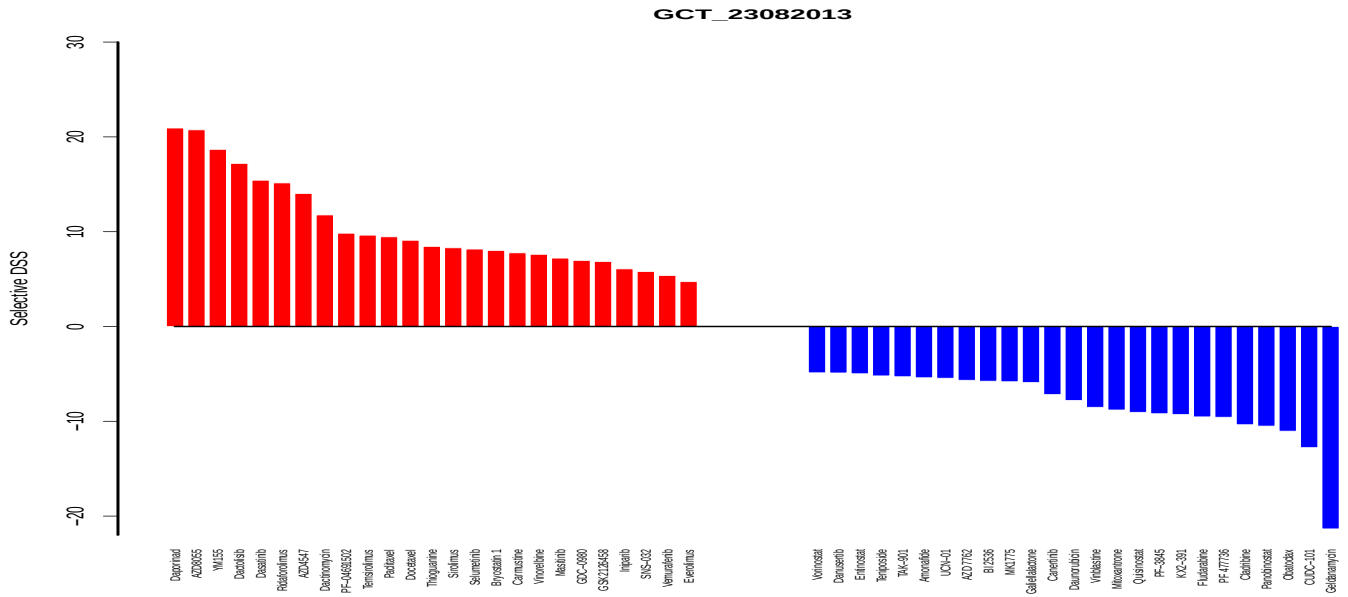
  of the tumor cells
- Drug sensitivity score-value (DSS)
  - Algorithm developed for

    comparing drug responses between drugs and between patients



Selective drug sensitivity score sDSS

- Differential activity of the drugs in GCT cells in comparison to healthy bone marrow cells

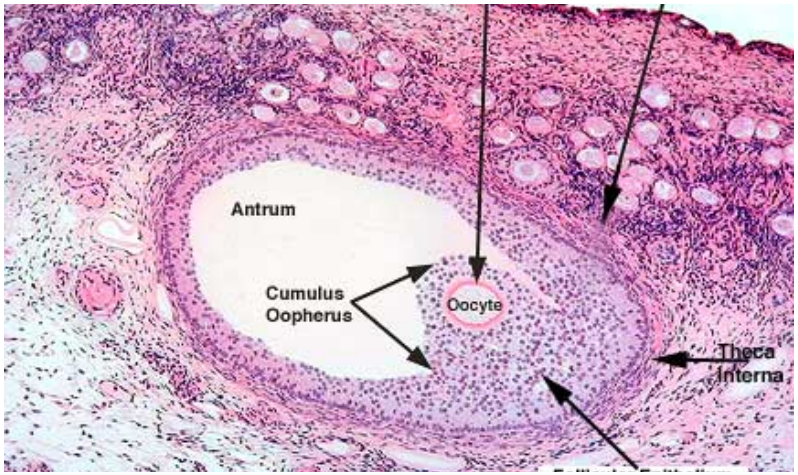


Unpublished data

Conclusions

- AGCT cells are more sensitive to paclitaxel than to bleomycin
- The most efficient compound in reducing cell viability of AGCTs was tyrosine kinase inhibitor dasatinib
- Dasatinib and paclitaxel seem to have synergy effect in AGCT cells when used in combination
- *In vivo* studies are needed

AGCT and hormones



Granulosa cells produce estradiol from androgens (aromatase enzyme active in granulosa cells)

AGCTs ”estrogen-dependent” – are they really?

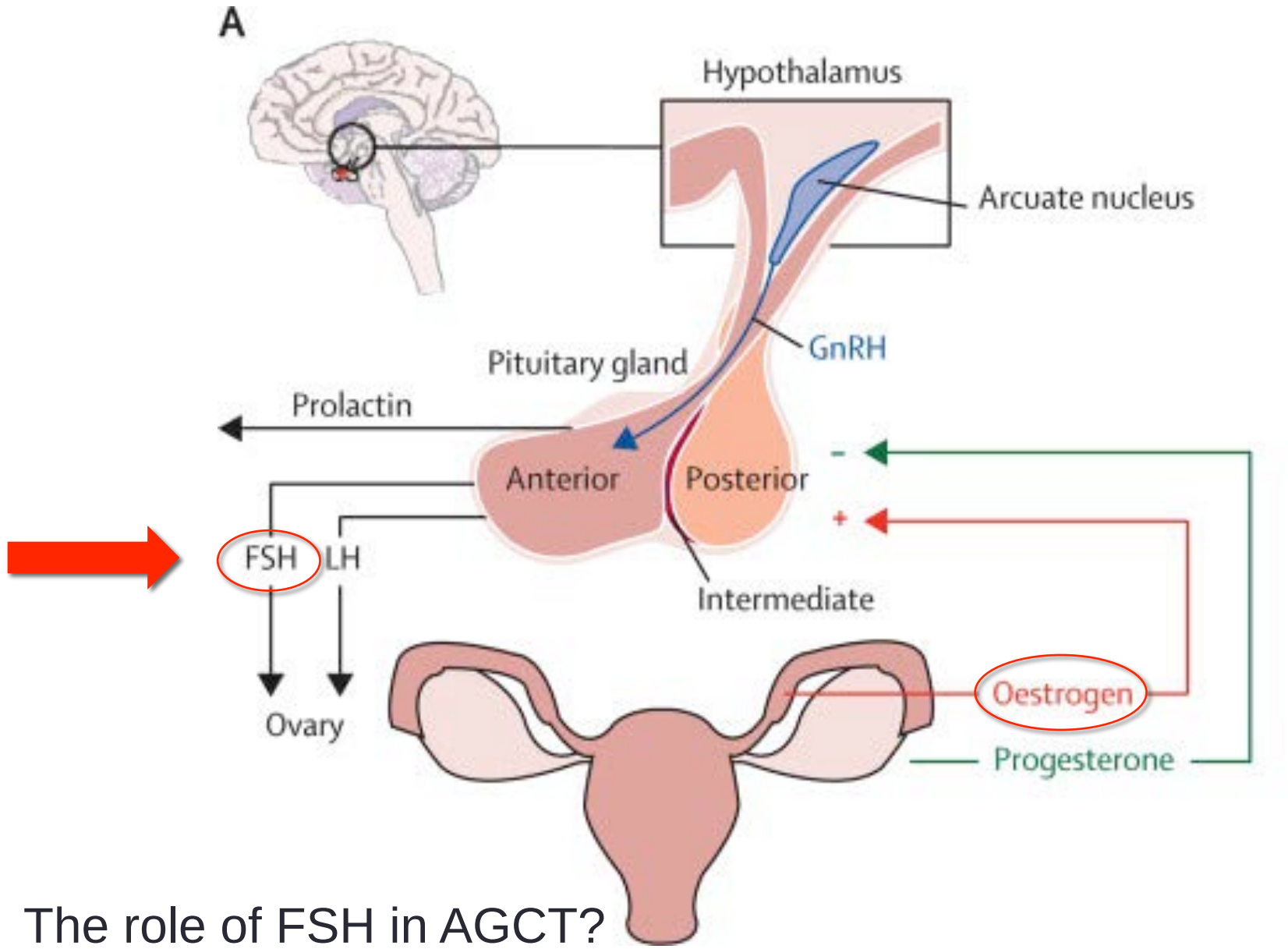
Clinical questions

- Estrogen replacement therapy after AGCT surgery?
  - Bryk 2015: HRT not risk for survival

- Aromatase inhibitors in AGCT, is there a rationale?

AGCT and hormones

- AGCTs secrete estradiol, but what does estradiol do to AGCT?
- Strong GPER intensity at primary diagnosis showed a significantly reduced overall survival (Heublein 2014)
- Does estrogen stimulate AGCT cell growth?
  - 17**β**-estradiol inhibits spreading of metastatic cells from granulosa cell tumors through a non-genomic mechanism involving GPER1 (Francois 2015)



The role of FSH in AGCT?

Future studies

- Hormonal characterization of AGCT
  - Clinical correlations
- The efficacy of aromatase inhibitors in AGCT
  - Can hormone receptors be used as predictive markers for hormonal treatments (clinical data)
  - Aromatase inhibitors in cell cultures
- AGCT cells and hormonal stimulations
  - Do we have to avoid ERT or not??

Thank you!

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