Vecchi anticorpi per nuove terapie biologiche

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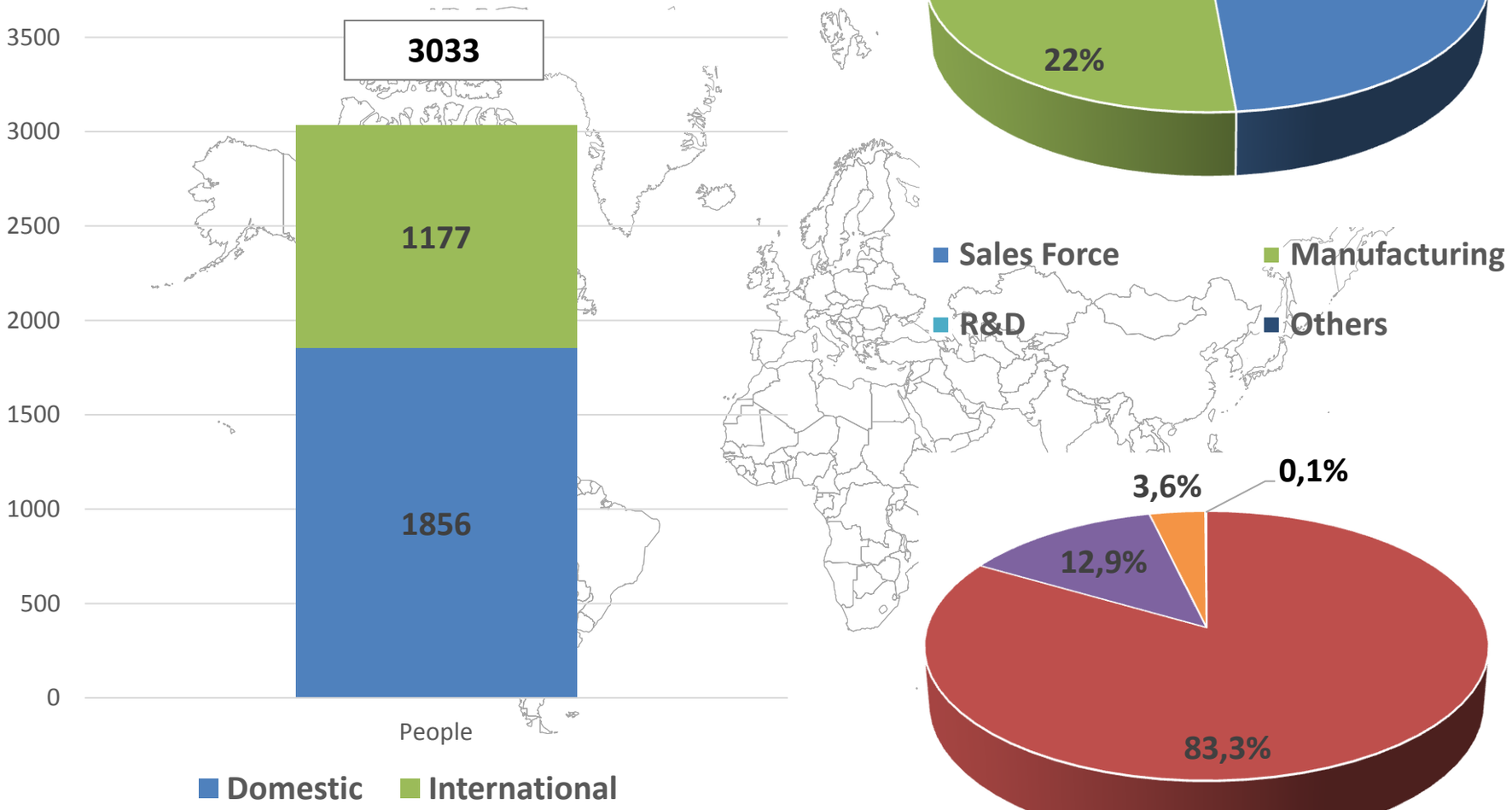
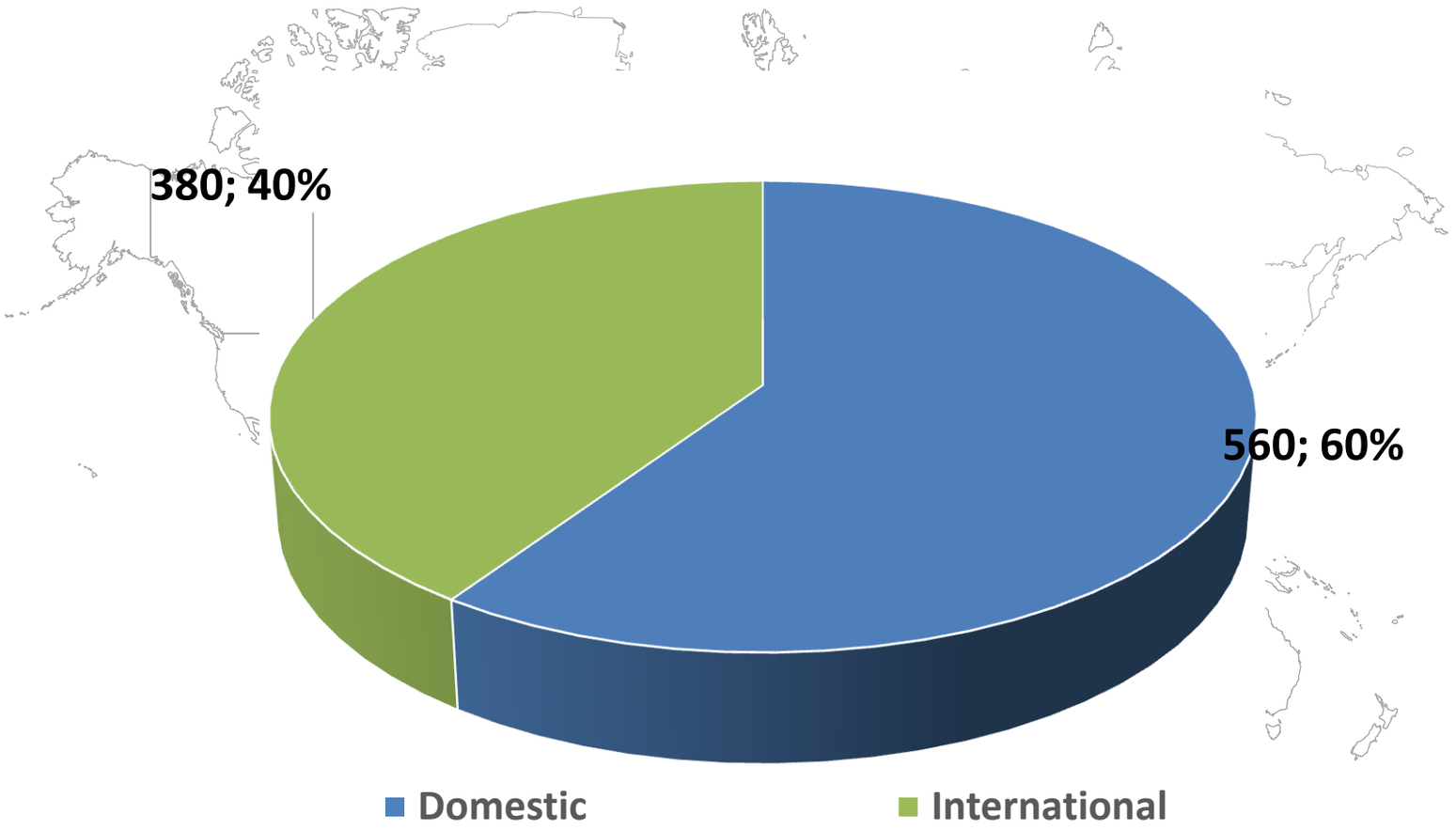
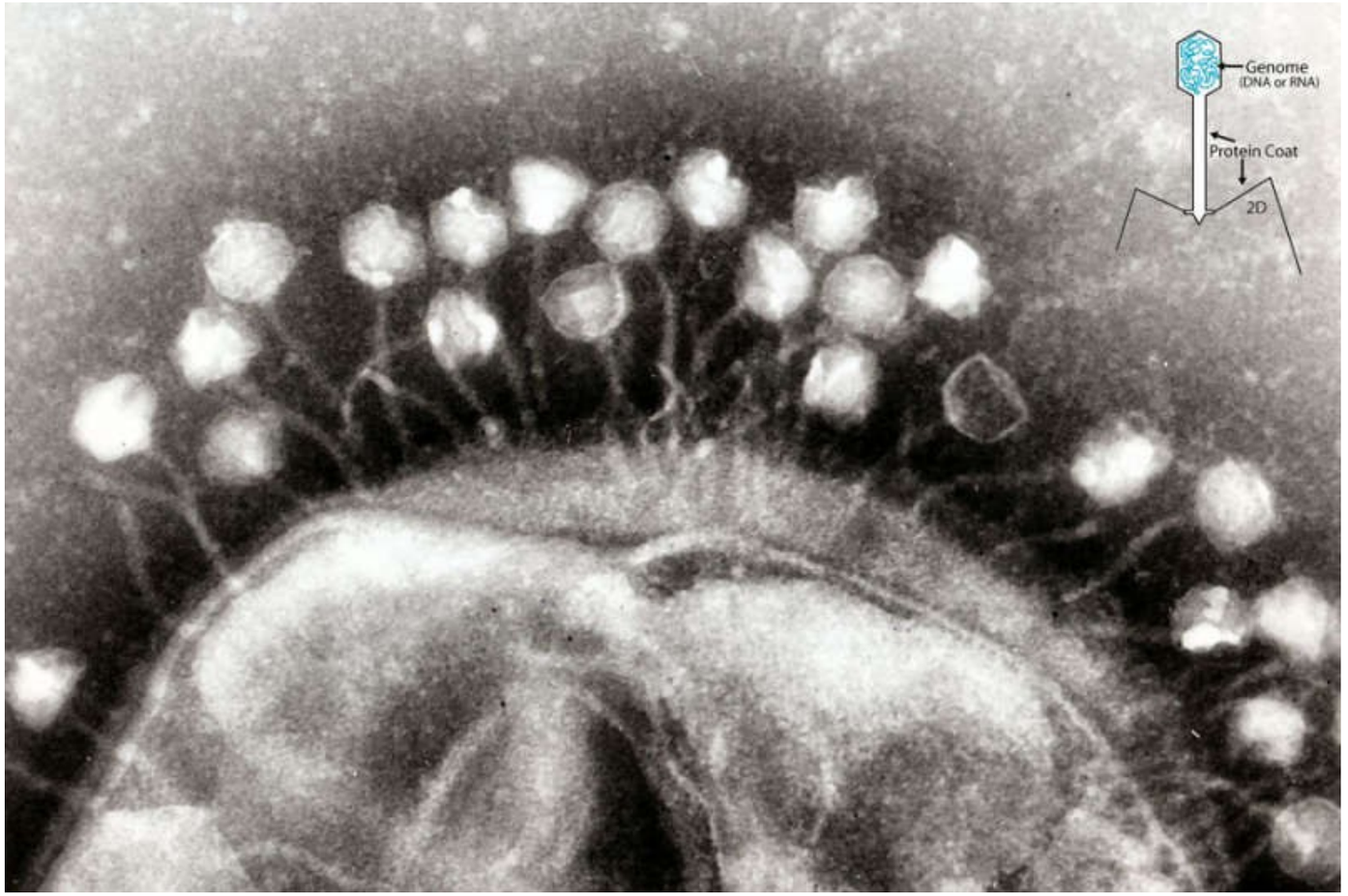
Alfasigma headcounts



Alfasigma 2016 Turnover: 940 M€



Phage



Bacteriophages or phages are viruses that infect bacteria

They represent most abundant biological entities on earth

They are GRAS

ST Biotech: competitive advantages on phage technologies

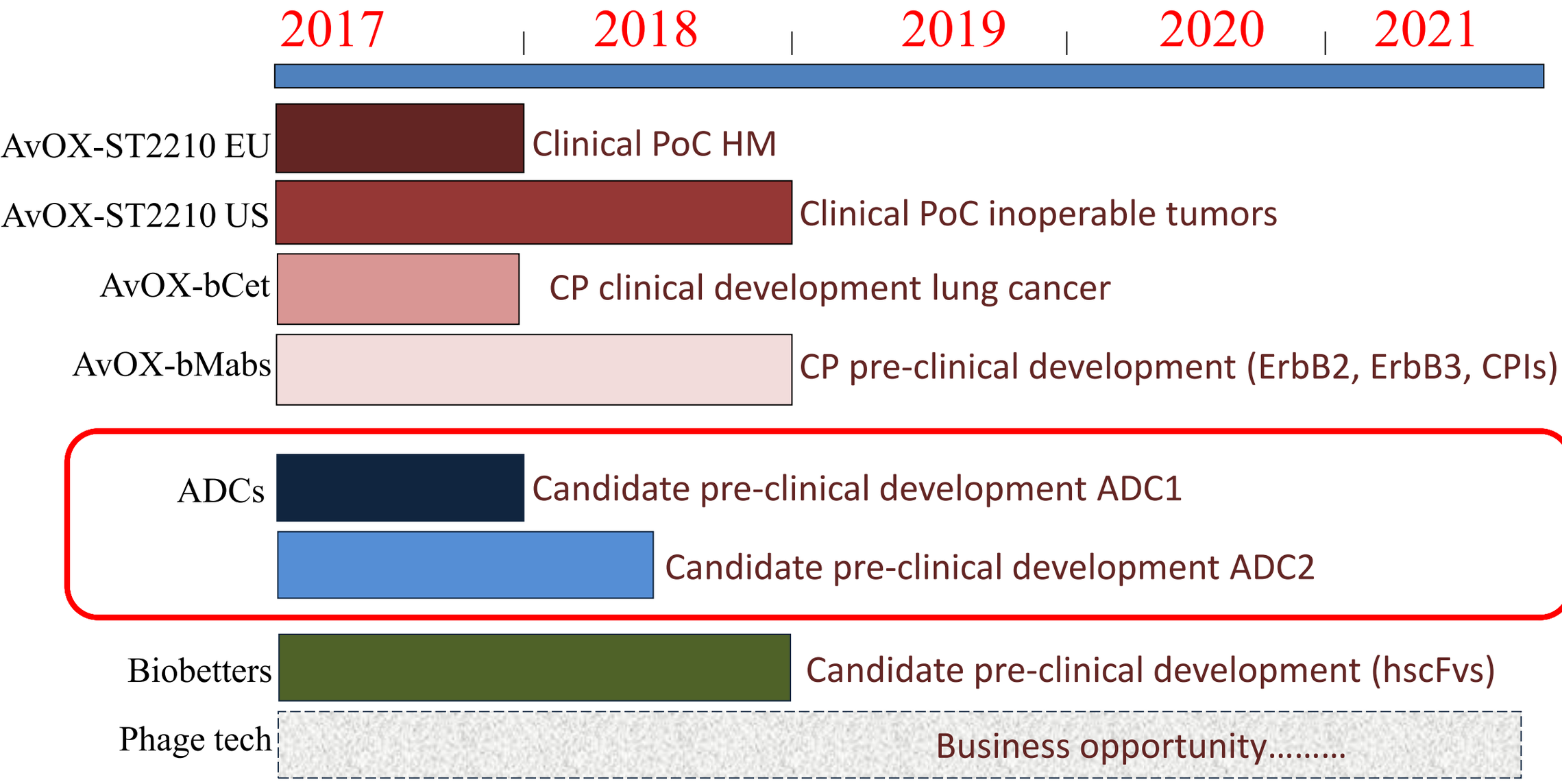
In house expertise:

1. Consolidated use of phage libraries for human antibody selection (Biobetters)
   - Patents
   - Several antibody selected and patented (i.e. recent anti-ErbB3, anti-PD1/PDL1)

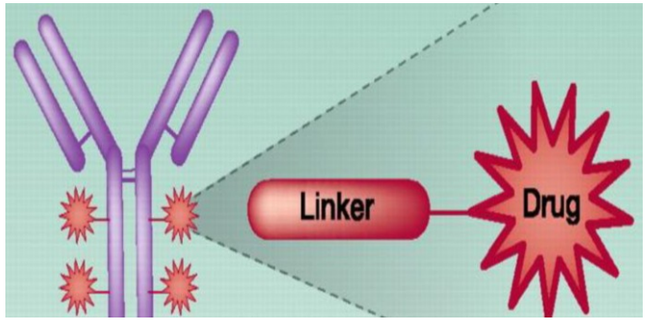
2. Possible easy connection with originator Countries where phage therapy is approved and marketed as OTCs (Russia)

To evaluate partnerships/collaborations

Biotech pipeline



ADCs: “old Mabs/new toxins” model



ST discontinued projects on small molecule chemotherapeutics

- **Blockbuster Mabs out of patent** with validated clinical targets (i.e. Cetuximab, Trastuzumab; biosimilars approved)

- **Thousands of Proprietary molecules** from different classes acting in the nano/micromolar range

Betting on crashing the ADC paradigm
“high payload toxicity good ADC efficacy”

ADCs: status 2Q2017

- Selected 2 ADC leads from a dozen different conjugates
- Pharmacology studies ongoing

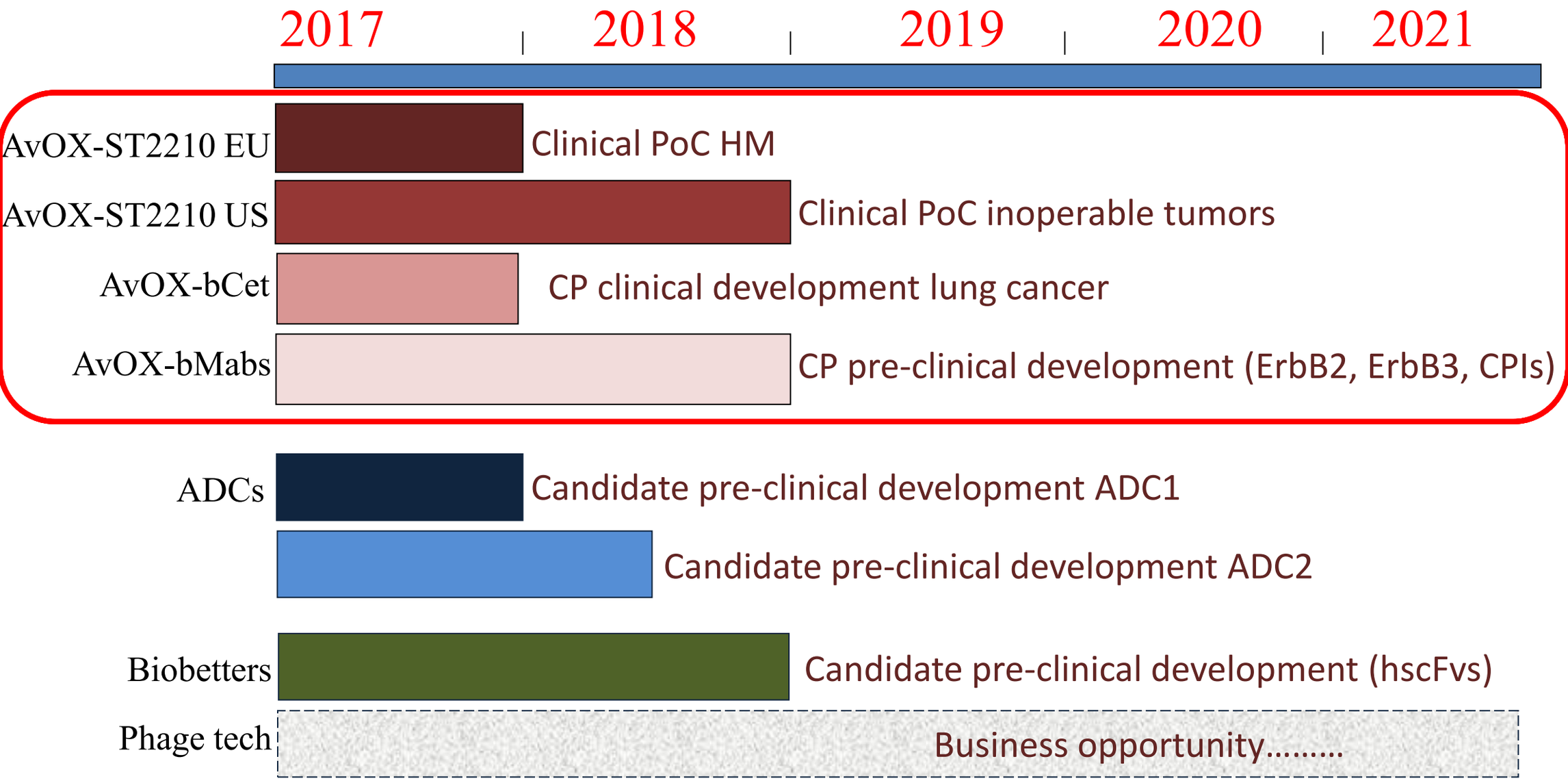
Active collaborations

- Siena University, Italy
- Toscana Life Science, Italy
- Takis, Italy
- Accelera, Italy
- Ephoran, Italy
- Crown Bioscience, USA
- University of Tallahassee, USA
- IrsiCaixa Institute, Badalona, Spain

Search for collaborations

- Formulation and delivery
- GMP development
- Pre-clinical regulatory package
- Biomarkers for selecting best target population
- Clinical development

Biotech pipeline

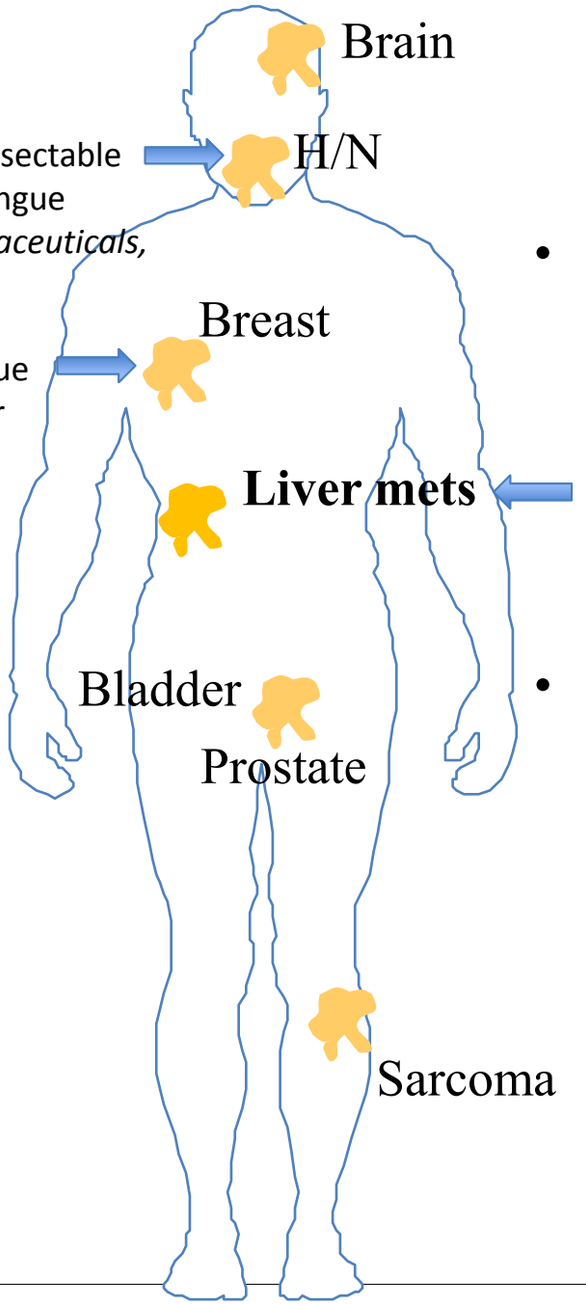


AvidinOX for RNT with radioactive biotin: status 2Q2017

Pre-clinical PoCs

Albertoni C, et al Radionuclide therapy of unresectable tumors with AvidinOX and 90Y-biotinDOTA: tongue cancer paradigm. *Cancer Biother Radiopharmaceuticals, 30(7):291-298, 2015*

De Santis R, et al AvidinOX for highly efficient tissue pre-targeted radionuclide therapy. *Cancer Biother Radiopharmaceuticals, 2010*



Clinical trials

- Phase I EU HM from CRC ^{177}Lu-ST2210 (ClinicalTrials.gov NCT02053324)
  13 patients treated:
  - no side effects
  - highly specific uptake
  - preliminary signs of efficacy
- Phase I various indications (MD Anderson Cancer Center, Houston, Tx, USA), FPI May 2017

Paul Ehrlich's magic bullets are finally coming of age?

Efficacy: **Increase TTP or OS Few months**

Safety: **Significant side effects**

Cost: **Very high**

Space for improvements

Efficacy of aerosol th
paralysis induced by

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Keywords: AvidinOX, Cetuximab, lung can
Received: July 09, 2014 Accep

ABSTRACT

Lung cancer, as well
from aerosol treatment.
nebulized drugs is fast,
that nebulized AvidinOX c
and SCID mice with adva
pre-nebulization with Av
growth at a dose lower
correlates with a strikin
biotinylated Cetuximab,
lines, leading to inhibitio
induction of massive lyso
of EGFR. Excellent tolera
AvidinOX and antibodies,

INTRODUCTION

Lung cancer is the leading cause
deaths and it has the greatest overall
among all cancers [1]. Many patient
with locally advanced disease and re
based therapies whose efficacy and tol
satisfactory. Lung cancer cells express Er
anti-epidermal growth factor receptor (E
antibodies (Mab) such as Cetuximab, P
Necitumumab have been widely used in
intravenous administration, showing lim
poor tolerability [2-4].

Aerosol may be an appealing deliv
cancer therapy because of site specificity
and excellent patient's compliance. Se
and clinical studies with nebulized ch

Intra-tumor AvidinOX all
biotinylated Cetuximab in

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ABSTRACT

For locally advanced and me
(HNSCC), the current clinical use
often associated to severe system
FaDu pharynx SCC cells, showi
Cetuximab (bCet) become active
tumor cells. AvidinOX-anchored b
specific inhibition of signaling, de
of EGFR. In the mouse model of
of AvidinOX allows anti-tumor ac
delivered, low dose bCet. Consist
is associated to induction of apo
AvidinOX is under clinical investig
tumors (ClinicalTrials.gov NCT0205
treatment of HNSCC in combinatio

INTRODUCTION

Head and neck cancer accounts for more
550,000 cases annually worldwide [1]. The m
overall survival for recurrent or metastatic head and
squamous cell carcinoma (HNSCC) remains less
one year despite a wide armamentarium of therap
approaches including anti-EGFR antibody Cetuxim
3]. The administration of Cetuximab in combination
radiotherapy and chemotherapy has shown modest su
improvement in patients with locally advanced
relapsed/metastatic cancer [3, 4] and such improve
is at expenses of increased local and systemic toxi
that deserve consideration and timely managemen
Therefore, there is a high medical need for improvin
cost/benefit ratio of current HNSCC treatments.

We recently described that anchoring biotiny
Cetuximab (bCet) on the surface of AvidinOX-conju

AvidinOX-anchored biotinylated trastuzumab and pertuzumab induce down-modulation of ErbB2 and tumor cell death at concentrations order of magnitude lower than not-anchored antibodies

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Keywords: *avidinOX, trastuzumab, pertuzumab, ErbB2, cancer*
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ABSTRACT

The oxidized version of Avidin, known as AvidinOX, was previously shown to link to tissue proteins upon injection or nebulization, thus becoming a stable receptor for biotinylated therapeutics. AvidinOX is currently under clinical investigation to target radioactive biotin to inoperable tumor lesions (ClinicalTrials.gov NCT02053324). Presently, we show that the anti-ErbB2 monoclonal antibodies Trastuzumab and Pertuzumab can be chemically biotinylated while maintaining their biochemical and biological properties. By using several and diverse experimental conditions, we show that when AvidinOX is conjugated to tumor cells, low antibody concentrations of biotinylated Trastuzumab (bTrast) or Pertuzumab (bPert) prevent internalization of ErbB2, induce endoplasmic reticulum stress, cell cycle arrest and apoptosis leading to inhibition of proliferation and ErbB2 signaling. Moreover, we found that the treatment is able to induce down-modulation of ErbB2 thus bypassing the known resistance of this receptor to degradation. Interestingly, we show that AvidinOX anchorage is a way to counteract agonistic activities of Trastuzumab and Pertuzumab. Present data are in agreement with previous observations from our group indicating that the engagement of the Epidermal Growth Factor Receptor (EGFR) by AvidinOX-bound biotinylated Cetuximab or Panitumumab, leads to potent tumor inhibition both *in vitro* and in animal models. All results taken together encourage further investigation of AvidinOX-based treatments with biotinylated antibodies directed to the members of the EGFR family.

INTRODUCTION

We previously reported that the oxidized version of Avidin, named AvidinOX, exhibits the distinctive property to form Schiff's bases with tissue proteins thus constituting a stable receptor for radiolabeled biotin [1–4]. This product is currently under investigation in phase I clinical trials for targeting ^{177}Lutetium-biotinDOTA (^{177}Lu-ST2210) [5] to inoperable tumor lesions and liver metastases (ClinicalTrials.gov NCT02053324). Previous data from our group also showed that AvidinOX can be employed for targeted delivery of diverse biotinylated therapeutics including cells [6] or antibodies. Particularly, several *in vitro* experiments indicated that AvidinOX-anchored anti-EGFR biotinylated antibodies like biotinylated Cetuximab (bCet) or Panitumumab (bPan), exert much higher inhibitory activity against EGFR$^+$ tumor cells compared to their original version. *In vitro* results were shown to correlate with anti-tumor activity of low bCet doses, intraperitoneally injected in mice with AvidinOX-treated human larynx carcinoma xenotransplants [7]. In a severe metastatic model of lung cancer, delivery by aerosol of extremely low doses of bCet was shown to control tumor growth and significantly improve survival, when administered after nebulized AvidinOX [8].

EGFR shares structural and functional properties with other members of the receptor family (HER2/ErbB2, HER3, HER4) all having roles in cancer development and drug resistance [9, 10]. Specifically, ErbB2 is the most relevant oncogenic receptor in breast and a key player in

AvidinOX active collaborations

Clinical development
Ospedale Latina, Italy
Sant'Andrea Rome, Italy
Ospedale Mestre, Italy
Vienna hospital, AU
MD Anderson Cancer Center, Tx, USA

Targeting pharmacology
Takis, Rome, Italy
Turin University, Italy

Immunology
La Sapienza Univ, Rome, Italy
Takis, Rome, Italy

GMP
Areta, Varese, Italy
Chelab, Treviso, Italy

Chemical/physical
Naples Univ, Italy
Rome Univ, Tor Vergata, Italy
Turin Univ, Italy
Toscana Life Science, Italy
Parma Univ, Italy
Ronzoni Institute, Milan, Italy
UPO, Alessandria, Italy

Radiochemistry
ABX, Austria

To find collaborations is not an option
Thank you!!!