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Introduction to AXL, bemcentinib and its application to COVID-19

BerGenBio's bemcentinib selected for fast-tracked UK Government study

29 April 2020

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Management presenting team today

Richard S. Godfrey, *Chief Executive Officer*

- Pharmacist / MBA – joined BerGenBio in 2008 as CEO
- Formerly CEO Aenova Inc., USA
- Previously Managing Director DCC Healthcare, earlier Eli Lilly, Reckitt Benckiser, Catalent
- 28 years industry experience, led and managed multiple international drug development and commercialization partnerships

Prof. James Lorens, *Founder and Chief Scientific Officer*

- Professor University of Bergen Medical School
- 30 years biotech research experience, academic biomedical research positions at Stanford University and University of Bergen
- Former Director Oncology R&D, Rigel Inc. (San Francisco, CA)
- The first to recognize that Axl kinase is an essential mediator of cancer development (EMT)

Prof. Hani Gabra MD, PhD, *Chief Medical Officer*

- MD Oncologist – joined BerGenBio in 2019
- Former VP Clinical Development Astra Zeneca UK.
- Professor of Medical Oncology at Imperial College London and Honorary Consultant in Medical Oncology at Imperial College Healthcare NHS Trust
- 20 years clinical / cancer biology research at Imperial College London.

BerGenBio corporate overview

World leaders in understanding AXL biology

AXL mediates immune evasion, therapy resistance, metastasis, & viral infection.

Pipeline opportunities in multiple cancers, viral infection and fibrosis

3 selective AXL inhibitors in clinical development

Bemcentinib,
AXL-antibody tilvestamab, AXL ADCT601*

Monotherapy and combinations with immune-, targeted and chemotherapies

Biomarker correlation across programme, parallel CDx development

Bemcentinib Phase II clinical trials:
AML (mono, **AML** (chemo-combo), **NSCLC** (KEYTRUDA combo), **COVID-19** (mono)

Resourced to deliver significant milestones

Listed on Oslo Børs: BGBIO

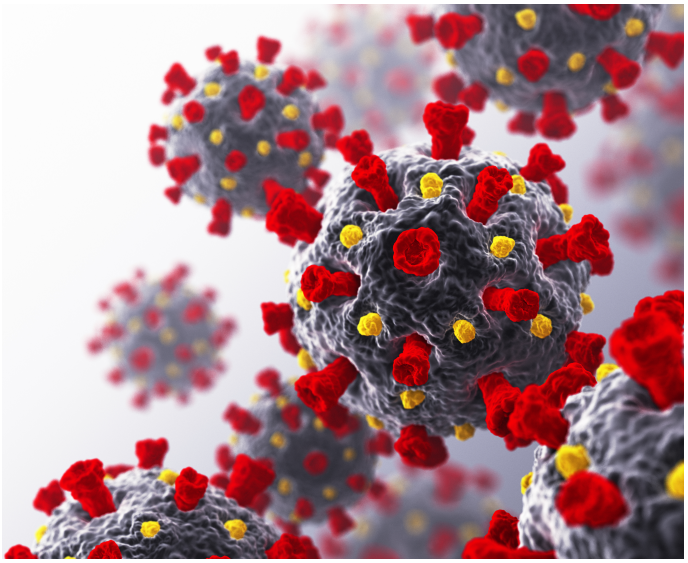
Clinical trial collaborations with Merck, UK NIHR and leading academic centres

38 staff at two locations:
HQ & R&D in Bergen, Norway;
Clinical Development in Oxford, UK

*AXL antibody out licensed to ADC Therapeutics SA

BerGenBio's bemcentinib selected to be fast-tracked as a potential treatment for COVID-19

- Preclinical data suggest that bemcentinib is potentially useful for the treatment of early SARS-CoV-2 infection, as it selectively inhibits AXL kinase activity
- Bemcentinib selected as the first candidate to be fast-tracked in a new UK national multi-centre randomised Phase II clinical trial initiative to investigate potential treatments for hospitalised COVID-19 patients
- ACCORD (**AC**celerating **C**OVID-19 **R**esearch & **D**evelopment platform) study is funded by the UK Department of Health and Social Care and UK Research and Innovation
- Study is a collaboration between the UK Government Scientific Office, the NIHR's Biomedical Research centres and clinical research company IQVIA
- Professor Tom Wilkinson is the academic lead of ACCORD-2, based at the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre
- The study will test 120 patients across 6 UK NHS hospital trusts, with the first patients due to be treated imminently



Protocol title: A Multicentre, Seamless, Phase 2 Adaptive Randomisation Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalised Patients

Rationale:

There are currently no approved therapeutic agents available to treat coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 disease, and there is an urgent public health need for rapid development of such interventions. This adaptive platform study is designed to rapidly assess multiple candidate agents as treatments for COVID-19. Candidate drugs that are initially assessed as being efficacious will be moved from an evaluation (pilot) stage to a confirmatory stage, with candidate agents being added to and removed from the study on an ongoing basis, depending on the results of their evaluation. Patients to be included in the study will be hospitalised and may require either supplemental oxygen, noninvasive ventilation or high flow oxygen devices, or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Objectives:

Stage 1: To evaluate the efficacy of candidate agents as add-on therapies to standard of care (SoC) in patients hospitalised with COVID-19 in a screening stage.

Stage 2: To confirm the efficacy of identified efficacious candidate agents in patients hospitalised with COVID-19 in an expansion stage.

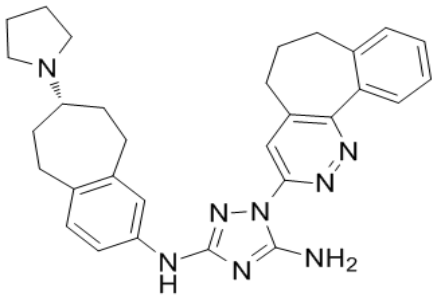
Endpoints:

- Time to clinical improvement of at least 2 points (from randomisation) of patients stage 3, 4 or 5 on a 9-point category ordinal scale, or live discharge from the hospital, whichever comes first (this will also define the “responder” for the response rate analyses).

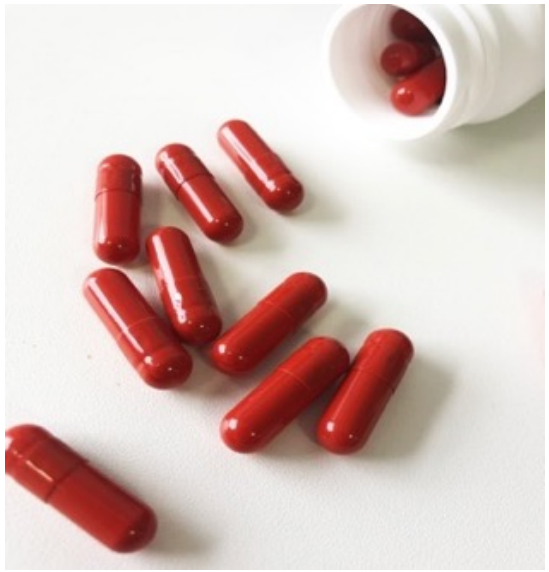
9-Point Category Ordinal Scale:

0. Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalised – mild disease, no oxygen therapy
4. Hospitalised – mild disease, oxygen by mask or nasal prongs
5. Hospitalised – severe disease, noninvasive ventilation or high flow oxygen
6. Hospitalised – severe disease, intubation and mechanical ventilation
7. Hospitalised – severe disease, ventilation and additional organ support – pressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)
8. Death

Bemcentinib, a first-in-class, potent, oral, highly selective AXL inhibitor



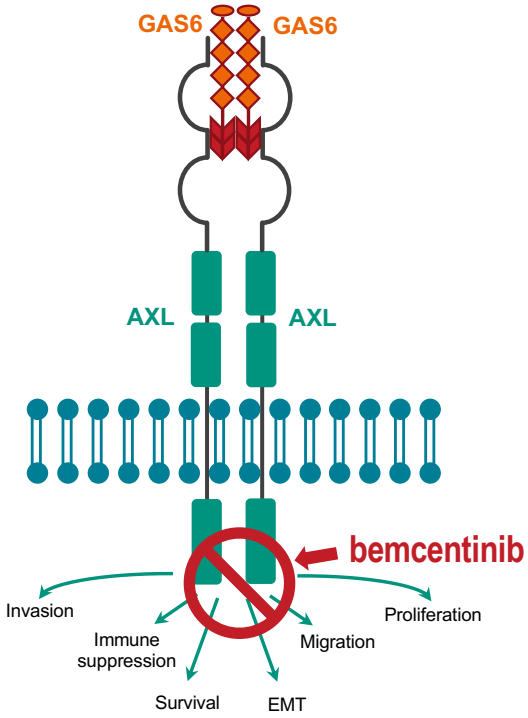
- ✓ IC_{50} = 14 nM
- ✓ Uniquely selective for AXL
  - ✓ 50-100 fold selective *cf.* TAM kinases



- ✓ CMC scaled for regulatory filing
- ✓ Size 0 100mg HPMC capsules
- ✓ 3 years stability confirmed

- ✓ Once daily oral dosing
- ✓ Already trialed in >300 patients
- ✓ Favourable safety profile supports use in first line, high risk fragile patients
- ✓ Safety and tolerability profile supports use in combination with other drugs
- ✓ MOA is synergistic with other therapies enhancing response
- ✓ Global regulatory exposure with Fast Track Designation by FDA
- ✓ IMP available in stock for immediate clinical trial use

AXL Biology



- AXL a receptor tyrosine kinase that is important for regulating innate immune cells.[1]
- AXL levels are elevated by cellular stress and is strongly associated with inflammatory diseases including cancer and fibrosis.[2]
- AXL drives cancer progression, immune evasion, and resistance to targeted therapies.[3]
- AXL is a key suppressor of the type I interferon response and is targeted by viruses to block the anti-viral immunity.[4]
- AXL is used by several different enveloped viruses (e.g. Ebola, Zika) to enter cells.[5]
- Bemcentinib potently inhibits SARS-CoV-2 infection of cells.[6]
- A lung cancer patient currently under treatment with bemcentinib who was high risk for COVID19 reported a mild Covid-19 infection.[7]

[1]Lemke Cold Spring Harb Perspect Biol 2013; [2]Zagórska Nat Immunol 2014, Ludwig Cancer Res 2018, Espindola, Am J Respir Crit Care Med. 2018;[3]Gay, Br J Cancer 2013; [4]Chen Nat Microbiol 2018; [5]Moller-Tank Virology 2014; [6]W.Maury, unpublished;[7]BerGenBio, unpublished

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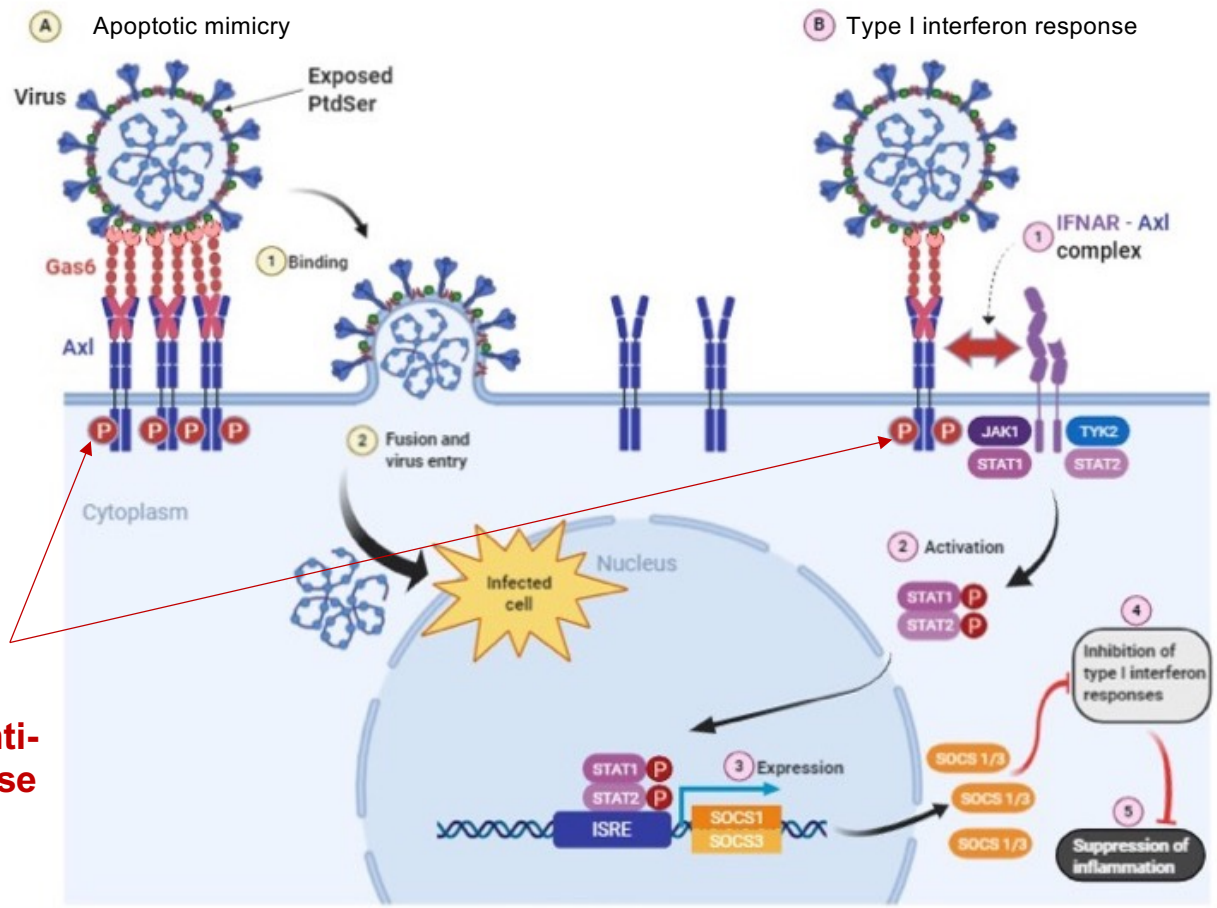
AXL is targeted by enveloped viruses to enter cells and dampen the viral immune response

Enveloped viruses display phosphatidylserine that is recognized by GAS6, the AXL receptor ligand, that mediates viral entry through “apoptotic mimicry”.

bemcentinib blocks AXL-dependent viral entry and enhances anti-viral interferon response



Viral-mediated AXL receptor activation dampens type I interferon responses, a key anti-viral defence mechanism for all cells

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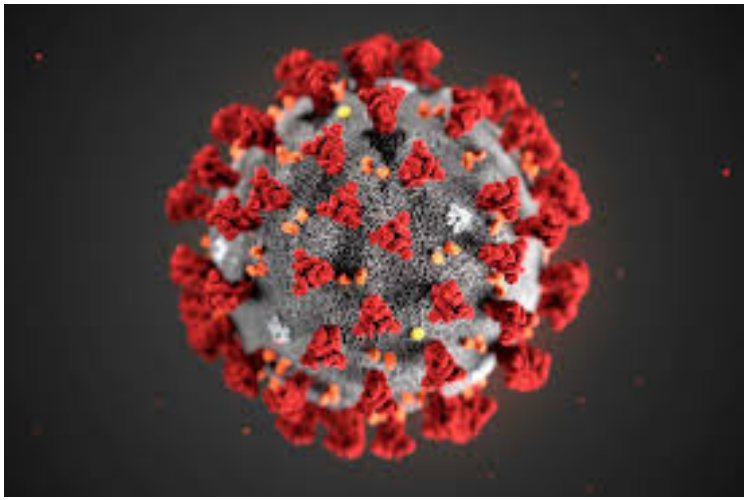
Summary & next steps

- Mechanistic and preclinical research supports rationale to treat COVID-19 with selective AXL inhibition
- ACCORD study aims to get an early indication of whether potential drug candidates could save the lives and improve the outcomes of the most vulnerable patients with COVID-19
- Top line data from the Phase II study will readout within a few months
- If results are positive, bemcentinib will advance rapidly into the large-scale Phase III trials currently in progress across the UK
- If successful, bemcentinib would ease pressures on hospital intensive care units, and ultimately treat thousands of patients
- We will provide timely updates on trial progress



Background published data

AXL mediates viral entry through “apoptotic mimicry” and suppresses the anti-viral type I interferon (IFN) response

AXL promotes the infection of a wide range of enveloped viruses including pox-, retro-, flavi-, arena-, filo-, and alpha-viruses (Shimojima 2006, Brindley 2008, Meertens 2012, Dowall 2016, Meertens 2017).

Viral particle binding via GAS6-AXL potently activates signal transduction through its tyrosine kinase domain to suppress type I interferon (IFN) signaling and facilitate viral replication (Bhattacharyya 2013, Meertens 2017).

AXL increases viral infection through two mechanisms:

1) enhanced viral entry through “apoptotic mimicry”; and
2) suppression of anti-viral type I interferon (IFN) responses

AXL mediates viral entry through “apoptotic mimicry” and suppresses the anti-viral type I interferon (IFN) response

AXL signaling suppresses viral-induced IFN responses via SOCS1/3, leading to increased viral replication in infected cells and decreased anti-viral defenses of neighboring cells (Huang 2015, Chen 2018, Strange 2019).

Therapeutic AXL receptor inhibition ameliorated pulmonary pathology resulting from primary viral infection in experimental models, indicating an important role for AXL within the lung (Shibata 2014).

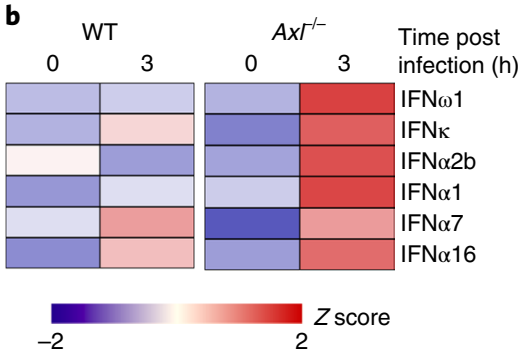
> During primary respiratory syncytial virus (RSV) infection, AXL inhibition increased the number of IFNg–producing T cells and NK cells, suppressed RSV replication and whole lung levels of IL-4 and IL-13.
>
> The lethal effect of intrapulmonary H1N1 infection inflammation was reduced by AXL inhibition. AXL inhibition in infected mice increased the number of IFN-b–producing macrophages and dendritic cells and suppressed neutrophil infiltration.

AXL-null mice are resistant to ZIKA pathogenesis likely due to a combination of reduced virus entry and enhanced IFN responses (Hastings 2019), **indicating a potential role for AXL inhibitors as therapeutics during viral infection.**

AXL is a unique type I interferon (IFN) response checkpoint

- IFNR signaling induces AXL expression[4,5]
- AXL is a critical negative feedback regulatory mechanism for TLR-induced type I interferon (IFN) responses in myeloid (dendritic cells, macrophage), NK and tumor cells[1-4].
- AXL is an IFN checkpoint: AXL signaling blocks IFNR signaling via SOCS1/3 and TBK1[5,6].
- AXL on dendritic cells is targeted by viruses (e.g. Zika) to abrogate IFN responses and inhibit anti-viral immunity[7].

AXL inhibition enhances type I interferon gene response to viral infection



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3. *Cañadas et al., Nat Med. 2018 Aug;24(8):1143-1150*
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Bemcentinib showed effect against lethal EBOV infection in animal models conducted by PHE

viruses

MDPI

Article

Antiviral Screening of Multiple Compounds against Ebola Virus

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Abstract: In light of the recent outbreak of Ebola virus (EBOV) disease in West Africa, there have been renewed efforts to search for effective antiviral countermeasures. A range of compounds currently available with broad antimicrobial activity have been tested for activity against EBOV. Using live EBOV, eighteen candidate compounds were screened for antiviral activity in vitro. The compounds were selected on a rational basis because their mechanisms of action suggested that they had the potential to disrupt EBOV entry, replication or exit from cells or because they had displayed some antiviral activity against EBOV in previous tests. Nine compounds caused no reduction in viral replication despite cells remaining healthy, so they were excluded from further analysis (zidovudine; didanosine; stavudine; abacavir sulphate; entecavir; JB1a; Aimspro; celgosivir; and castanospermine). A second screen of the remaining compounds and the feasibility of appropriateness for in vivo testing removed six further compounds (ouabain; omeprazole; esomeprazole; Gleevec; D-LANA-14; and Tasigna). The three most promising compounds (17-DMAG; BGB324; and NCK-8) were further screened for in vivo activity in the guinea pig model of EBOV disease. Two of the compounds, BGB324 and NCK-8, showed some effect against lethal infection in vivo at the concentrations tested, which warrants further investigation. Further, these data add to the body of knowledge on the antiviral activities of multiple compounds against EBOV and indicate that the scientific community should invest more effort into the development of novel and specific antiviral compounds to treat Ebola virus disease.

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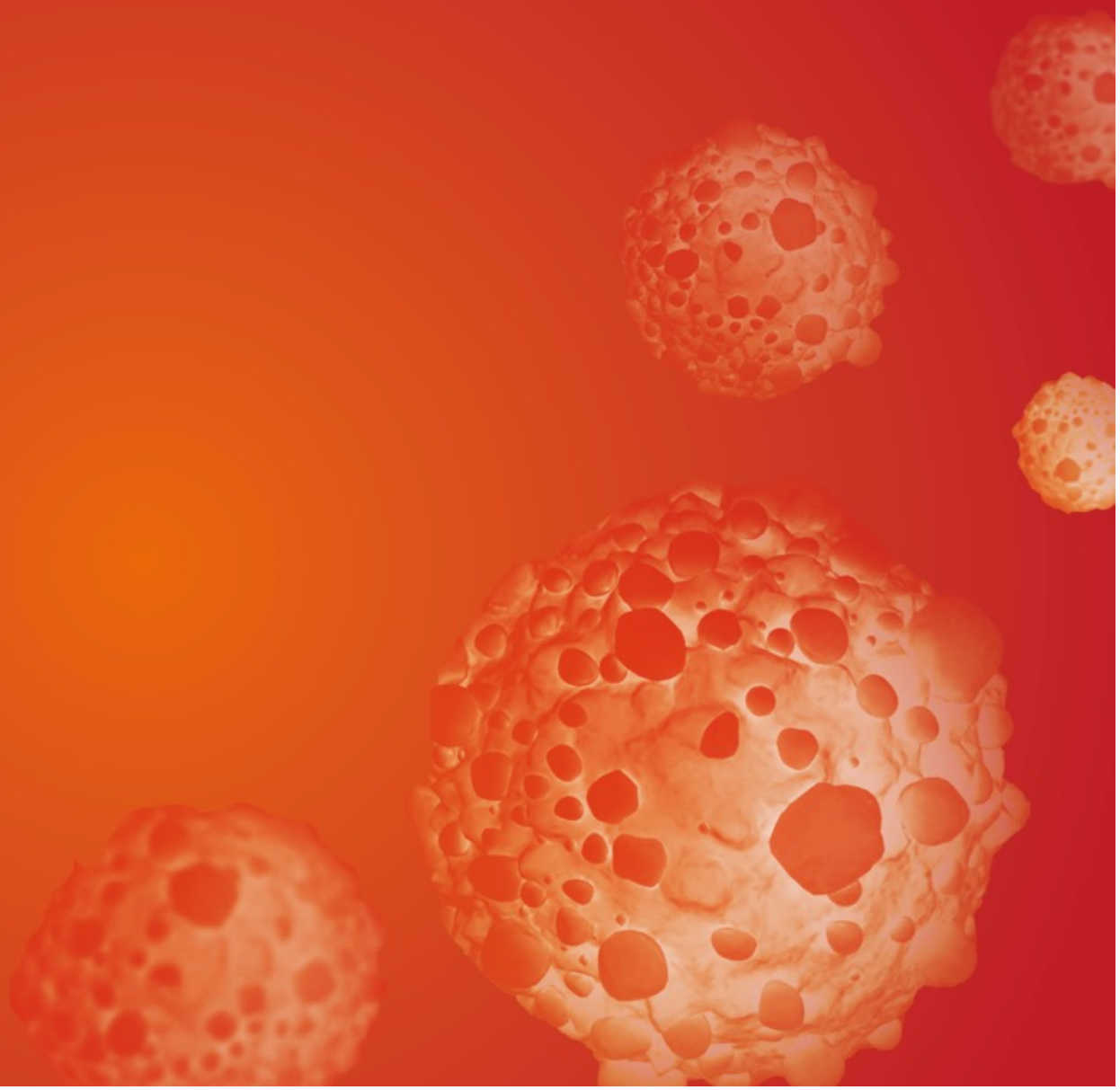

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- Demonstration that GAS6-AXL complexes tether enveloped viruses to cells, activating AXL and dampening type I interferon responses.

Chen J *et al.* AXL promotes Zika virus infection in astrocytes by antagonizing type I interferon signalling. *Nat Microbiol* 2018 *3*:302

- Key article showing that Zika virus targets AXL on dendritic cells to block type I interferon responses including several type I interferon genes and IFN-stimulating genes.

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Hastings *et al.* Loss of the TAM Receptor Axl Ameliorates Severe Zika Virus Pathogenesis and Reduces Apoptosis in Microglia *iScience* 2019 *13*:339

- Report showing that *Axl* knockout mice are resistant to ZIKV pathogenesis.

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- Report detailing the role of GAS6-AXL in Dengue viruses (DVs) infection.

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Demonstration that bemcentinib blocks ZIKA virus infection of glial cells but blocking AXL-mediated viral entry and dampened innate immunity.

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Shimojima M *et al.* Tyro3 family-mediated cell entry of Ebola and Marburg viruses. *J Virol.* 2006 *80*:10109

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Bemcentinib:

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- Bemcentinib blocks aggressive traits of pancreatic cancer&enhances activity of gemcitabine.
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- Axl inhibition via bemcentinib reprograms immunological microenvironmentoIncreased proliferation and activation of CD4 and CD8
- Bemcentinib and PD-1 blockade act synergistiaclly

Mode of Action & Biomarkers

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- Immune checkpoint inhibitors are most effective against T-cell inflamed tumours. Non-T-cell or T-cell excluded tumours remain a significant barrier to treatment.
- Axl identified as a key mediator of immune evasion and experimental evidence demonstrates Axltargeting leads to greater anti-tumour immune response post radiotherapy.

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- Proteases known as sheddases cleave the extracellular domain of several receptor tyrosinekinases such as Axl generating soluble Axl (sAxl).
- Plasma levels of sAxl are predictive of patient response to standard of care BRAF&MEKinhibitor therapy and could be used for patient stratification strategies.

Antony et al (2017) The GAS6-AXL signaling network is a mesenchymal (Mes) molecular subtype–specific therapeutic target for ovarian cancer.*Science Signalling*

- Axl particularly abundant in ovarian cancer subtype designated as mesenchymal (Mes)
- Axl co-clustered cMET, EGFR, and HER2, producing sustained extracellular signal–regulated kinase (ERK) activation in Mes cells
- Bemcentinib reduced tumor growth in chick chorioallantoic membrane model.

Kanzaki, R.,*et al.,*(2017) 'Gas6 derived from cancer-associated fibroblasts promotes migration ofAxl-expressing lung cancer cells during chemotherapy,'*Nature Scientific Reports,*Sept 6th.

- Tumor stroma microenvironment (TME) is comprised of cancer-associated fibroblasts (CAFs)which influence cancer cells such as non-small cell lung cancer (NSCLC).
- In a murine model, NSCLC treated with cisplatin induced an up-regulation of Gas6.
- NSCLC line H1299 migrated in response to Gas6.
- The CAF cell line LCAFhertexpresses GAS6 and can promote H1299 cell migration.
- Conclusion- CAF derived GAS6 promotes migration of Axl-expressing lung cancers.

Reviews

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